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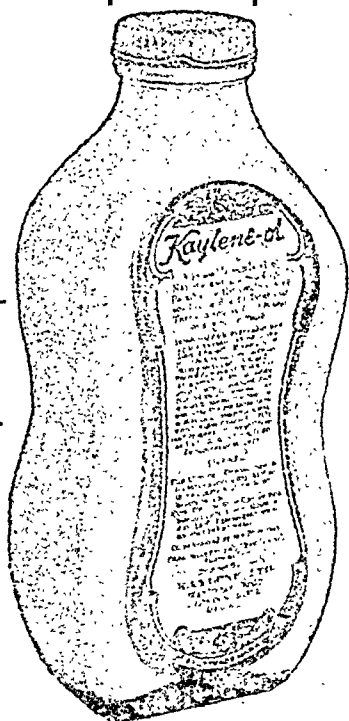
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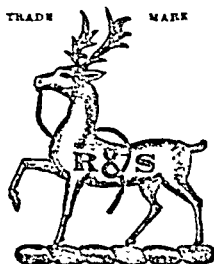
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Service.	Rank.	Pay.	Allowances. (Home rates.)		Pay plus allowances at Home rates.	
			Married.	Single.	Married.	Single.
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After 2 years on promotion to	<i>Flight Lieutenant</i>	422	230	119	652	541
Rising by increments after 2	" "	486	230	119	716	605
and 4 years to	" "	553	233	157	788	710
After 10 years total service on	<i>Squadron Leader</i>	553	233	157	788	710
promotion to	" "	812	233	157	1045	969
Rising by increments after 2,	" "	894	234	187	1128	1081
4, 6, 8 and 10 years to . . .	<i>Wing Commander</i>	894	234	187	1128	1081
By selection to	" "	1022	234	187	1256	1209
Rising by increments after 2	" "	1187	308	248	1443	1385
and 4 years to	<i>Group Captain</i>	1187	308	248	1443	1385
By selection to	<i>Air Commodore</i>	1298	362	309	1660	1607
By selection to	<i>Air Vice Marshal</i>	1624	428	370	2050	1994

ALLOWANCES AT STATIONS ABROAD

In addition to the current pay shown above, officers stationed abroad are provided with furnished quarters (with fuel and light) and rations, or allowances in lieu, and receive colonial and servant allowances. The present total of the allowances (including colonial and servant allowances) payable when provision in kind is not available is as follows :—

	EGYPT.		PALESTINE.		MALTA.		MALAYA.	
	Married.	Single.	Married.	Single.	Married.	Single.	Married.	Single.
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<i>Flying Officer</i>	£489	£226	£486	£226	£275	£131	£639	£283
<i>Flight Lieutenant</i>	439	226	453	226	276	131	639	283
<i>Squadron Leader</i>	489	278	453	280	275	147	639	312
<i>Wing Commander</i>	540	333	547	342	318	162	715	415
<i>Group Captain</i>	577	369	597	383	354	198	740	442

The married rates are payable only when the officer is accompanied by his family. If unaccompanied he is treated as unmarried for the purposes of his own accommodation, or allowances in lieu, and receives a consolidated allowance in respect of the separated family as follows :—

Flying Officer	£109 per annum.
Flight Lieutenant and Squadron Leader.	136 per annum.
Wing Commander and Group Captain	173 per annum.

Iraq and Sudan.—Families are normally not allowed in these countries, and officers are provided with accommodation, etc., for themselves and receive colonial and servant allowances. The present rates of colonial allowance amount to £142 per annum (Iraq) and £55 per annum (Sudan). In addition, married officers receive the consolidated allowance for separated families at the rate shown above.

Aden and Transjordan.—Families are only allowed at these stations if public marked quarters are available. Married officers accompanied by their families are accordingly provided with married accommodation, etc., and receive a servant allowance of 2s. a day and a colonial allowance of 10s. a day at Aden, and 7s. in Transjordan. All other officers are provided with unmarried accommodation and receive servant allowance of 2s. a day and colonial allowance of 5s. at Aden, and 3s. 3d. a day in Transjordan. In addition, married officers separated from their families receive the consolidated allowance at the rates shown above.

The rates of pay of the R.A.F. Medical Branch are fixed on an inclusive basis, and the fact that specialist pay and charge pay are not payable as separate emoluments was taken into account when the rates were fixed.

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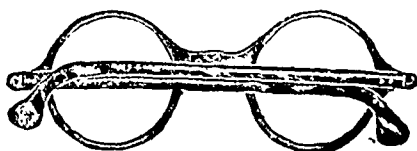
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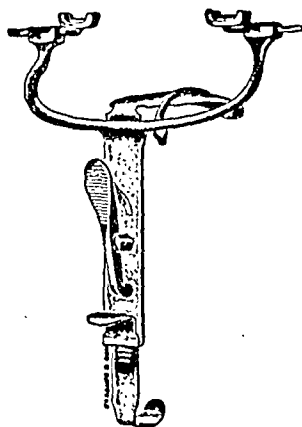
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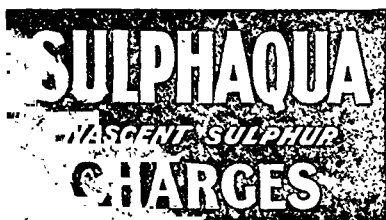
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Edinburgh Medical Journal

June 1932

STUDIES ON BLOOD AND TISSUE REACTIONS.

III. THE SPECIFICITY OF TISSUE AND BLOOD-REACTION.

By W. F. HARVEY and T. D. HAMILTON.

(From the Laboratory of the Royal College of Physicians of Edinburgh.)

(Continued from p. 310.)

OUR study has been chiefly concerned with reactions, as manifested by the advent or withdrawal of leucocytes or wandering cells in or from the blood, and their appearance at an injured spot. Even with this restriction the discussion comes to be very much that of the long debated and still debated subject of inflammation. It may be well to intimate that our conception of inflammation, as distinct from repair, is that of simple reaction to trauma. The controversy over this matter is perhaps not so acute as it used to be. Some of the earlier views with regard to inflammation, however, and the development of theories of reaction have much present-day interest and a definite bearing on our work. Ziegler,^{1, 2} could not decide upon a definition of inflammation and contented himself with a simple account of the features of inflammation. In his view, "the phagocytosis in the course of an inflammation represents a purely accidental phenomenon which is often brought about for the simple reason that both mobile cells and also material to be ingested are present." Thoma,³ who was distinctly inclined to press for the non-specific character of inflammation, seems to have become a little unsettled in his opinions on the purely traumatic character of inflammation, possibly with the appearance of the work of Metchnikoff on chemiotaxis, and to have finally described it rather comprehensively as essentially a traumatic, toxic, or

W. F. Harvey and T. D. Hamilton

infective lesion. According to Metchnikoff,⁴ Stahl,⁵ with his demonstration in myxomycetes of attraction and repulsion under the denominations positive and negative trophotropism, and Pfeffer,⁶ who found positive chemiotaxis of the female organs of cryptogams for the spermatozooids, were the originators of the idea of chemical cytotropism to definite localities. The application of the theory to pathology was essentially the work of Metchnikoff⁷ himself. "When I first put forward the biological theory of inflammation," he says, "I expressed the idea that this reaction is effected by the intermediation of a physiological continuity between the cells of the connective tissue, those of the endothelial wall, and the leucocytes, which form a complete chain and play the principal part in the inflammation of vertebrates. All the other phenomena in inflammation may be regarded as means to facilitate the access of phagocytes to the injured part"; and again: "The sensibility of the phagocytes is not an hypothesis which can be rejected at will but an established fact," says Metchnikoff in reply to Fraenkel.⁸ "Whether they possess powers of thought and volition . . . is quite beside the question, though we are justified in considering that they possess a germ of these qualities. . . ." Metchnikoff considerably modified his theory in later years. This modified theory is very clearly given by Adami.⁹ Much of this later pronouncement was superimposed upon the earlier more cellular doctrine, as a result of Ehrlich's publications. The final reconciliation, so to speak, of the phagocytic and humoral doctrines of immunity and reaction was effected by Almroth Wright with the development of his theory of specific opsonic activity. Wright's¹⁰ own views, however, have become decidedly of a non-specific doctrinal character with the enunciation of his "Code No. 3." "For while established notions," says Wright, "prejudice us against the idea of vaccination conferring a non-specific protection, reflection puts out of court alternative suggestions." We do not go further into this interesting discussion, as we are not concerned with immunity but with cellular reaction in tissues and in blood to the introduction of irritants or the application of trauma to the body. It has been necessary to make reference to these doctrines to support and explain our own contention that the commonly held idea of infection is that of a somewhat specific reaction depending on the type of irritant concerned. This may be only indirectly expressed and

Studies on Blood and Tissue Reactions

even be accompanied by statements of non-specificity, but it is implied in much histological description and in the findings of hæmatology. The tubercle follicle, the syphilitic gumma, the pyogenic organisms, granulocytic stimulation, malarial and protozoal monocytoses, typhoid lymphocytosis, defence reaction and so on, are everyday terms. "Leucocytic variations differ both in degree and in kind in infective suppurations, in infective exudations and in non-infective suppurations" (Hickling).¹¹ Our experiments have a special bearing on the question of specificity or singularity of cellular reaction. These have consisted of an examination of the reaction in the subcutaneous tissue three weeks and six weeks after injection in the rabbit of a large variety of substances. One special investigation of the effect after injection of kieselgur extended over a long period and included examinations within a few hours, week by week and month by month, up to one and a half years. The slow progress *both of these experiments themselves and of the histological examination* required caused us finally to resort to intraperitoneal injections in mice with examination of peritoneal fluid and of blood for cell reaction. These were much more easily carried out and results obtained more rapidly.

The rabbits injected subcutaneously with a suspension of kieselgur are in some ways the most interesting because of the long period over which they were observed. Kieselgur may be regarded as an irritant of an almost purely mechanical kind and representing a material which is not capable of being digested by cells nor of being broken down by body fluids. The appearances are given in some detail, partly for their own interest and partly because they serve as basis of comparison, for the time intervals used, of the various irritants or stimuli employed in the investigation. The Table on pp. 352-353 sets out in order and in brief what the general nature of these appearances was.

We had set out originally on an investigation into the development and ultimate fate of the foreign body giant cell. At the end of eighteen months there was little sign of the demise of this cell and with the accidental death of the animal, which would have carried our expectation of its disintegration to a two-year period, we should have had to embark on a still more lengthy experiment. It seemed to us possible too that a state of quiescence or dormant continued existence, a symbiosis with its indigestible contents might be the real fate of the

W. F. Harvey and T. D. Hamilton

TABLE I.

Tabulation of histological appearances in the rabbit after subcutaneous injection of a 0.5 per cent. sterile suspension of kieselgur in normal salt solution.*

Interval after Injection.	Short Description of Appearance of Tissue Injected.
0 hours . . . { (immediate)	Disruption of collagenous fibres; some hæmorrhage; deposition of naked diatom fragments in the tissues.
12 hours . . . { 24 " . . . }	Invasion of injected area by polymorphs, forming with diatom es and collagenous tissue a confused mass.
36 hours . . . {	Some phagocytosis of polymorphs at the periphery of the central mass by monocytes† and some endothelial proliferation with formation of new capillaries.
48 hours . . . { 60 " . . . }	A central mass of debris, amorphous except for diatoms and nuclei or nuclear remains of polymorphs. At the periphery of this mass, swelling and increase in number of fibroblasts; swelling and proliferation of endothelium with formation of new capillaries; numerous monocytes; phagocytosis of polymorphs, erythrocytes, blood pigment and amorphous granular material.
84 hours . . . { 7 days . . . }	Some invasion of amorphous central mass at its margins by monocytes and fibroblasts. Around the central mass fibroblast proliferation and circumferential layering of fibrous tissue; large monocytes abundant, some containing diatoms. No evidence of any fresh accession of polymorphs and no sign of giant cells.
2 weeks . . . { 3 " ‡ . . . }	Central mass necrotic, still unorganised; less compact. Around the central mass are monocytes. Small giant cells have made their appearance, with 1 to 5 nuclei, and contain diatoms and amorphous material. Fibroblasts are active and some are in mitosis. The circumferential layering of fibrous tissue is well marked (encapsulation). Capillary vessels are numerous.
4 weeks . . . {	Central mass mainly amorphous but showing some invading cells—monocytes, giant cells and fibroblasts, these last with oval or long nuclei and surrounded by definitely fibrillated collagen. Diatoms can still be seen to be free in the centre along with ill-defined debris. Around the central mass, besides monocytes, giant cells with ingested diatoms, and fibroblasts, there is marked capillary budding. Manifest fibrous encapsulation.

* The injection was found to be situated between the muscular layer of the skin known as the panniculus carnosus and the fascial aponeurosis covering the deep muscles.

† We use the term monocyte for what is otherwise designated, according to function or origin as phagocyte, macrophage, clasmatoocyte, histiocyte, polyblast, etc.

‡ This is an important interval because it is that at which an examination of the injected tissues was made for a large variety of injected substances, calcium phosphate, agar, tubercle bacilli, staphylococci, etc.

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TABLE I.—*continued.*

Interval after Injection.	Short Description of Appearance of Tissue Injected.
6 weeks* 2 months	The central portion is no longer apparent as an amorphous mass. In its place we have large giant cells full of diatoms and having their many nuclei arranged at the periphery of the cell. There is penetration of the mass by capillary blood-vessels and by collagen producing active fibroblasts, so as to separate it up into compartments of giant-cell tissue. Around the central mass or masses capillary budding is not so evident and there is layering of fibrous tissue which is looser in immediate proximity to the central mass and denser a little further away. The bulk of the central mass has diminished, probably through elimination of removable or digestible material, and it is becoming disposed in line parallel with the skin surface.
4 months	The central mass is much diminished in bulk and width and the disposition into compartments and into parallelism with the surface is pronounced. It is fully cellular and well vascularised. The giant cells are distinctly larger with anything up to 50 or 100 peripheral nuclei. Their cytoplasm is granular and contains diatoms. Around these segregated masses is a fairly dense but quiescent fibrous tissue. Not much, if any, evidence of lymphatic dispersion of diatom containing cells.
6 months	The appearance in this case is of an earlier stage than that which has been described for the 4-months' interval. Such appearances are only to be expected in a series where in some cases doses may have been larger or the transformation has not been uniform throughout.
8 months	The linear disposition of masses of large giant cells in more or less discrete compartments, surrounded by a dense but ordinary fibrous tissue without much sign of cellular reaction are the general features of this stage. Between the giant cells are found monocyctic cells of very much the same appearance, except for size and number of nuclei. There is no sign of breaking up of giant cells or any release of their diatom contents. A few foci of lymphocytic cells are now apparent interspersed among the giant cells.
12 months	Evidently a large injection. Appearances at places of a very much earlier stage, even to the presence of a small polymorph central area in one part.
18 months	The giant cells and monocytes are present as far as one can see unchanged and contain diatoms. Separation of the masses of giant cells from one another is still more marked by fibrous tissue and it looks as if this might continue with increased compression of masses of giant cells. A marked feature is now the appearance of lymphocytes with their dark staining nuclei, in foci and to some extent diffusely. The reaction area generally seems reduced in extent.

* This is an equally important interval for the same reason as in that of the 2-weeks' interval.

foreign body giant cell. Diminution of bulk of the necrotic material associated with the injection of the kieselgur was undoubtedly evident with time, but was this due to phagocytic activity or have we here a case analogous to the sequestrum of bone, in which, according to Greig,¹² osteoclasts as foreign body giant cells remove the dead material "to the best of their poor ability . . . and far less efficiently than the serum in which the sequestrum is bathed"? In the course of our routine examination of pathological material we have seen a preparation of peritoneal tissue from a case which had been injected with paraffin four years previously and in which microscopical examination showed masses of paraffin still enfolded or guarded by foreign body giant cells. A case of persistence of giant cells is published by Fried and Stone¹³ of about two years' duration. One wonders too whether the intracellular carbon of lung anthracosis, the intracellular pigment of the tattoo mark, and many such examples that might be cited, are instances of long drawn out cell life with strange cytoplasmic contents. Although we had not succeeded in our original intention, it was still obvious to us that we had in this series of trials a valuable demonstration and a standard by which to gauge the cellular reaction of tissue to introduction of irritant. The realisation of this fact led us to proceed further to a determination of the different types of cell reaction which might be produced by the introduction into the tissues of a variety of irritant substances, mechanical, chemical and organismal. The main substances which we have used for this purpose in an experiment of subcutaneous injection were calcium phosphate, cholesterol, hæmoglobin, hæmatin, starch, indian ink, paraffin, agar, alcoholic eosin, tubercle bacilli and staphylococci. It was not possible to extend our trials in this case to one and a half years and we chose periods of three weeks and six weeks for our examination of the tissues, expecting to find the reaction somewhat peculiar to each irritant according as it was soluble or insoluble, lipoid or non-lipoid, of tissue origin or entirely foreign, organismal or non-organismal. It would serve no useful purpose to set down the reactions in these cases in full detail. It will suffice here to say that, *mutatis mutandis*, the reactions were remarkably similar in all cases as to sequence of events with the kieselgur controls, so far as that could be judged from the use of our two arbitrary periods of time after injection. Some comments may be made on the differences

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in reaction, such as did occur, with some of these substances, as these are probably what represent the reactions peculiar to groups of substances. The organisms used in suspension were killed by sterilisation. Both the tubercle bacilli and the staphylococci produced subcutaneous abscess formation with protuberance of the skin surface. Giant cell formation was much more noticeable with calcium phosphate, hæmoglobin, hæmatin, cholesterin, starch and agar than with tubercle bacilli or staphylococci. As regards these last two organisms, it was noticeable that for the periods selected, there were actually more and larger giant cells in the reacting tissue round the central polymorph-necrotic mass for staphylococci than for tubercle bacilli. In some of the cases the central necrotic mass had already disappeared in three weeks' time, and the place of this was occupied by a wholly cellular organised and organising tissue with fibroblasts, collagen, capillary endothelium, a few well-formed undegenerated polymorphs, monocytes in large number and giant cells with inclusions. This is the case, for example, with calcium phosphate. Here the picture was rather like a later stage of kieselgur reaction. It may be that calcium phosphate was not very irritant even mechanically; its degree of solubility would be greater than kieselgur. In the case of indian ink there was the same picture, but an exaggerated strung-out linear appearance as in some of the later stages of kieselgur reaction and a suspicion that the material might be being removed or washed along lymphatic channels. In some cases, and notably in that of paraffin, the cellular reaction was minimal. Here, even at three weeks there was an absence of polymorphs altogether, and very little of the monocyte-fibroblast-endothelial reaction. Paraffin was contained within giant cells within a fibrosed area. The central necrotic mass, persistence of polymorph infiltration and general evidence of continuance of an acute local irritation were the characters of the reaction at the end of the six weeks' trial of both tubercle and staphylococcus.

We gained the distinct impression and, with our other evidence in support, have come finally to the conclusion that the reaction was the same for all irritants, that it differed in regard to acuteness and duration of the respective phases with consequent variation in the attainment of a stable and quiescent condition. In fact we found for all these irritants what Medlar and Kastlin¹⁴ found for the tubercle bacillus, when they consider

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it more plausible that "the response on the part of the different leucocytes is due to the type of damage produced in the tissue than to the tubercle bacillus as a foreign body." We anticipate, however, in enunciating this conclusion, for we did not feel justified on the strength of the experimentation we had done to proceed at once to the generalised theorem. The histological procedure of following out reaction of tissues to irritants was a slow one, and we devised a technique which got over this difficulty, and at the same time we investigated the concomitant blood-cell reaction in the peripheral circulation for the various irritants used. We chose the peritoneal cavity as our locality of irritant introduction and the differential cell proportions in the peritoneal fluid as measure of tissue-cell reaction. The intravenous mode of introduction has an advantage in so far as the test material comes to rest locally without the complication of any trauma used in its deposition. It has, however, the decided disadvantages of too widespread a possible localisation, an essentially intravascular localisation and, again, the disadvantage that the method does not permit of repetition of examinations at successive intervals without the use of separate animals. A word is necessary, however, in further justification of our choice of the peritoneal cavity or, as we call it, large lymph space. It is easily entered and, if one is careful, there is an absence of complicating reaction due to hæmorrhage or to damage of local tissues. It is, moreover, not so much the reaction associated with repair that we are studying as the reaction of wandering cells of the blood and loose connective tissue to specific irritants. We eliminate, by the use of the peritoneal cavity, the phenomena of reparative fibroblastic and vascular reaction. We have no reason to suppose that the cells which wander into the peritoneal cavity and are found in the peritoneal fluid are in any great measure different from those entering the tissue and lymph spaces of the subcutaneous tissue with the advent there of an irritant substance. Two quotations from (1) Sabin, Doan, and Forkner¹⁵; and (2) Maximow¹⁶ may serve as our support for this view:—(1) "For the study of the direct effect of any substance upon the connective tissue the intraperitoneal route has certain advantages owing to the nature of the omentum"; and (2) "The tissue of the serous membranes is a peculiar variety of the common, loose, irregularly arranged connective tissue," and again, "The resting wandering cells of the common,

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irregularly arranged, connective tissue belong to a vast cell system distributed all over the body and termed at the present time . . . the system of histiocytes (reticulo-endothelium)." But, above all, our choice of tissue and of animal, the mouse, enabled us to repeat observations and obtain results at intervals without the necessity of multiplication of animals and without the delay and uncertainty of preparation of histological material for examination.

Technique.—The test materials were so far as possible suspended in normal salt solution which, and distilled water, are, according to Sabin, Doan and Forkner (*loc. cit.*), "the diluents of choice" for an assay of biological activity of the substances used. These substances were, as far as possible, used in a strength of 0.5 per cent. The amount of suspension or, as the case may be, test fluid injected was at first 1 c.c., but was afterwards reduced to 0.5 c.c., because it was found that in a small animal like a mouse 1 c.c. of fluid in the abdominal cavity resulted in an inconvenient degree of dilution of the exudate cells and a corresponding difficulty in obtaining sufficient numbers for counting in the films made of the peritoneal fluid. Immediately after the injection the abdomen was massaged so as to set free and distribute the cells of omentum and mesentery which constitute with the general peritoneum the reacting tissue in our experimentation. Following the first injection and the corresponding massage, peritoneal fluid was immediately withdrawn by means of a capillary pipette as the sample to represent the tissue condition, *qua* cells, before the specific substance injected has had time to exert its special action. At each subsequent examination 1 c.c. or, as the case may be, 0.5 c.c. of simple normal salt solution was injected prior to the massage and prior to the removal of the sample of peritoneal fluid. Films were made of the samples obtained, stained with Leishman's stain, and a differential count of the cells made.

The classification of types of cells which we used was into neutrophils, lymphocytes, monocytes, eosinophils, basophils, and macrophages. In the mouse we did not find any basophils. The macrophage we define as a specially large uninucleated cell, from 20 to 40 μ or more in diameter with vacuolated basophilic cytoplasm and often with cellular inclusions in the shape of neutrophils, erythrocytes, bacteria or unrecognisable fragments. A control experiment was the reaction to the injection of normal salt solution only. The intervals of examination

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were, unless otherwise stated, of 0, 4, 24, 72 hours; 14 days and 28 days, and it is to these intervals that the successive percentage figures given below under the respective cell types refer.

NORMAL SALT SOLUTION.—*Neutrophils*—7.5, 61.8, 35.3, 21.2, 13.7, 0.6. *Lymphocytes*—66.4, 34.7, 47.6, 65.3, 68.2, 87.6. *Monocytes*—22.5, 34.7, 3.8, 5.0, 8.1, 4.2. *Eosinophils*—1.4, 1.8, 5.4, 2.1, 1.9, 5.3. *Macrophages*—2.2, 0.3, 7.9, 6.4, 8.1, 2.3.

KIESELGUR.—*Neutrophils*—9.9, 63.9, 42.9, 39.6, 16.7, 7.7. *Lymphocytes*—78.1, 31.0, 31.7, 42.2, 79.5, 86.2. *Monocytes*—6.7, 3.2, 14.6, 6.7, 1.6, 2.5. *Eosinophils*—2.0, 1.5, 2.0, 2.9, 1.6, 1.9. *Macrophages*—3.3, 0.3, 8.8, 8.4, 0.5, 1.7.

ALEURONAT.—*Neutrophils*—2.4, 46.6, 13.4, 5.4, 13.7, 6.7. *Lymphocytes*—80.9, 44.2, 54.2, 63.8, 79.9, 77.8. *Monocytes*—9.1, 6.3, 13.8, 18.8, 4.4, 1.9. *Eosinophils*—1.5, 0.6, 7.5, 0.6, 0.7, 0.3. *Macrophages*—6.1, 2.3, 11.4, 1.2, 13.3.

B. TYPHOSUS (living). *Neutrophils*—0.7, 72.0, 65.3, 38.3, —, 3.7. *Lymphocytes*—81.0, 20.8, 7.4, 31.2, —, 67.3. *Monocytes*—4.9, 1.5, 11.0, 10.4, —, 2.0. *Eosinophils*—10.5, 5.7, 5.0, 10.9, —, 20.0. *Macrophages*—2.8, 0.0, 11.2, 9.2, —, 7.0.

STAPHYLOCOCCUS (living). *Neutrophils*—6.2, 59.6, 46.7, 19.1, 12.9, 9.9. *Lymphocytes*—69.1, 33.3, 49.4, 41.4, 76.7, 63.4. *Monocytes*—22.1, 4.5, 0.9, 13.1, 5.9, 10.9. *Eosinophils*—1.4, 1.0, 1.5, 2.1, 0.9, 0.9. *Macrophages*—1.1, 1.5, 1.4, 24.3, 3.4, 14.9.

BENZOLE.—*Neutrophils*—15.2, 70.2, 58.6, 25.7, 36.1, 18.3. *Lymphocytes*—74.9, 25.9, 31.7, 40.6, 42.7, 62.4. *Monocytes*—2.1, 0.6, 3.1, 1.3, 1.2, 3.7. *Eosinophils*—4.9, 2.7, 2.5, 7.3, 16.5, 10.7. *Macrophages*—2.9, 0.6, 4.1, 25.1, 3.5, 4.9.

B. TUBERCULOSIS.—*Neutrophils*—1.9, 59.9, 39.8, 50.9, 43.0, 11.1. *Lymphocytes*—85.2, 21.6, 32.6, 37.6, 50.7, 84.2. *Monocytes*—6.1, 1.3, 9.2, 1.9, 2.1, 3.9. *Eosinophils*—4.9, 17.3, 4.1, 4.1, 0.7, 0.3. *Macrophages*—1.9, 0.9, 14.3, 5.5, 3.5, 0.5.

NUJOL.—*Neutrophils*, 5.9, 32.5, 46.1, 46.5, 6.2, 2.6. *Lymphocytes*—77.5, 48.4, 41.6, 46.7, 88.4, 92.3. *Monocytes*—2.5, 2.5, 2.3, 0.5, 1.3, 0.4. *Eosinophils*—11.4, 15.5, 8.7, 5.4, 3.1, 4.5. *Macrophages*—2.7, 1.1, 1.3, 0.9, 1.0, 0.2.

INDIAN INK.—*Neutrophils*—3.9, 78.3, 66.0, 17.2, 4.9, —. *Lymphocytes*—85.4, 19.8, 29.1, 58.7, 85.7, —. *Monocytes*—1.9, 0.6, 0.6, 2.7, 1.7, —. *Eosinophils*—5.9, 0.9, 0.4, 5.9, 7.2, —. *Macrophages*—2.9, 0.4, 3.9, 15.5, 0.5, —.

B. MONOCYTOGENES (living, very weak suspension). *Neutrophils*—4.4, 35.1, 59.7, 33.4, 2.2, 3.1. *Lymphocytes*—87.8, 53.8, 30.7, 42.4, 88.1, 78.2. *Monocytes*—5.2, 5.6, 3.9, 11.1, 5.5, 9.8. *Eosinophils*—0.4, 1.3, 0.9, 0.8, 0.9, 0.7. *Macrophages*—2.2, 4.2, 4.8, 12.3, 8.2.

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These are somewhat complicated figures but have been set out in this way to avoid a very expanded table.

Allowance has to be made for some individuality in the animals used and for the variations of random samples, but in spite of these and in spite of a few surprise counts here and there we find on the whole a remarkable sameness of reaction throughout. This sameness is as much evident in the case of normal salt solution and nujol, or even simple entry of the abdomen with an injection needle, as it is with typhoid, tubercle, and staphylococcus. Aleuronat was greatly used in days gone by to give, on intrapleural injection, a neutrophil exudate. Here we see little evidence of its difference in this respect from any of the other irritants. It will also be remembered that nutrient bouillon used to be employed by intraperitoneal injection for the same purpose as aleuronat. We have not used nutrient bouillon in our series, but we have little doubt that in the mouse it would not act otherwise than have the irritants which we have selected for trial. We recognise the fact that for our own convenience, and for the multiplication of results, we have used a small animal like the mouse, which we contend probably gives us a strong reaction instead of the weaker one which would result from the use of a larger animal like the rabbit. We also recognise the fact that as compared with man, who is a "neutrophilic" blood animal, the mouse is what is called a "lymphocytic" animal. But we do not think that the general principle of the mere sequence of events is likely to have been greatly disturbed by our choice. We are not comparing the mouse with man, but using it as a reactive animal to a variety of reagents or irritants which might be expected to elicit something of the nature of specific cellular responses from blood and tissues. The sequence of events then seems to be the occurrence of neutrophilic increase coupled with relative lymphocyte diminution in the very earliest stages which is followed by lymphocyte increase and relative neutrophil diminution attaining to or exceeding the original proportions by the 14th or 28th day after the introduction of the irritant. Macrophages, as we have defined them, exhibit marked increase during the early and middle portion of the trial, to return to normal proportions by the 28th day. The monocyte and the macrophage are, in our opinion, cells of very much the same stock and the former would seem to pass by gradation into the latter. In fact our own work with "segregation apparatus"

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and mitochondrial stains and a study of the illustrations to Cappell's¹⁷ work on this subject would lead us to unite the lymphocyte, the monocyte, and the macrophage into the one group. But in this research it is the blood and tissue-cell reaction we deal with, and not that fascinating study of the parentage of the cells involved.

Having now made the point of the sameness of the type of reaction of the peritoneal lymph space and its surrounding tissues to the introduction of irritants we may look at the type of peripheral blood-cell reaction to these intraperitoneal injections. In this case we have the total counts, that is to say, the reaction of the totality of leucocytes as well as the percentage counts resulting from intraperitoneal injections of irritants. These may be set out for the same series and in the same way as for the peritoneal fluid. The first set of figures is of the total leucocyte counts at 0, 4, 24, 72 hours, 14 days and 28 days, after which come the percentage figures for these same intervals in the case of the several types of blood cells.

NORMAL SALT SOLUTION.—13,000, 6250, 15,600, 13,400, 18,600, 18,000.
Neutrophils—25.5, 59.6, 32.5, 18.3, 12.0, 17.0. *Lymphocytes*—59.8, 37.7, 60.1, 77.3, 77.5, 75.5. *Monocytes*—12.7, 2.1, 5.9, 3.8, 6.6, 4.7. *Eosinophils*—2.0, 0.6, 1.5, 0.6, 3.9, 2.8.

KIESELGUR.—7650, 5200, 8150, 11,900, 11,800, 7750. *Neutrophils*—27.5, 27.5, 60.4, 44.0, 43.0, 29.3, 26.8. *Lymphocytes*—63.6, 33.7, 44.5, 49.7, 68.4, 71.1. *Monocytes*—8.9, 5.9, 11.0, 6.4, 2.3, 1.6. *Eosinophils*—0, 0, 0.5, 0.9, 0, 0.5.

ALEURONAT.—12,450, 7250, 13,750, 27,750, 21,850, 36,750. *Neutrophils*—11.7, 48.1, 26.4, 27.4, 19.6, 10.6. *Lymphocytes*—80.2, 45.8, 62.2, 64.9, 75.4, 84.1. *Monocytes*—8.9, 5.9, 11.0, 6.4, 2.3, 1.6. *Eosinophils*—2.0, 1.4, 3.9, 0.7, 1.2, 1.7.

B. TYPHOSUS (living).—26,050, 4400, 8650, 14,450, —, 20,900. *Neutrophils*—25.4, 45.5, 46.9, 19.9, —, 6.2. *Lymphocytes*—67.9, 45.5, 46.9, 19.9, —, 89.9. *Monocytes*—6.0, 8.7, 11.7, 17.0, —, 2.4. *Eosinophils*—0.7, 0.2, 5.9, 1.9, —, 1.5.

STAPHYLOCOCCUS (living).—23,750, 6250, 17,100, 18,000, 12,000, 18,150. *Neutrophils*—23.2, 47.0, 32.4, 25.4, 25.0, 24.7. *Lymphocytes*—64.7, 47.2, 60.3, 70.2, 65.4, 67.2. *Monocytes*—10.1, 5.3, 4.8, 3.2, 7.0, 7.0. *Eosinophils*—2.0, 0.5, 2.5, 1.2, 2.6, 1.1.

BENZOLE.—22,650, 7900, 10,050, 12,250, 17,100. *Neutrophils*—17.1, 52.6, 44.6, 43.2, 39.9, 34.5. *Lymphocytes*—80.8, 43.3, 48.3, 50.8, 55.5, 60.3. *Monocytes*—1.2, 3.5, 6.7, 3.6, 3.5, 3.0. *Eosinophils*—0.9, 0.6, 0.4, 2.4, 1.1, 2.2.

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NUJOL.—31,550, 20,400, 22,850, 41,175, 35,600, 19,950. *Neutrophils*—19.5, 28.6, 14.9, 28.2, 13.5, 17.7. *Lymphocytes*—78.1, 67.6, 81.8, 68.8, 83.8, 79.7. *Monocytes*—1.2, 3.2, 2.3, 1.5, 2.3, 1.5, 2.3, 2.6. *Eosinophils*—1.2, 0.6, 1.0, 1.5, 0.4, 1.0.

B. TUBERCULOSIS.—19,200, 4800, 8350, 12,550, 19,650, 14,050. *Neutrophils*—9.7, 29.8, 40.3, 48.2, 60.3, 25.2. *Lymphocytes*—87.3, 65.4, 51.4, 47.2, 34.9, 70.3. *Monocytes*—1.7, 3.4, 5.5, 3.7, 3.0, 2.6. *Eosinophils*—1.3, 1.4, 2.8, 0.9, 1.8, 1.9.

INDIAN INK.—16,900, 12,200, 23,900, 17,650, 28,500, 19,900. *Neutrophils*—38.3, 77.4, 33.3, 30.9, 30.1, 42.6. *Lymphocytes*—60.2, 21.8, 61.1, 64.8, 63.7, 52.6. *Monocytes*—0.9, 0.4, 0.9, 1.6, 2.4, 3.9. *Eosinophils*—0.6, 0.4, 4.7, 2.7, 3.8, 0.9.

B. MONOCYTOGENES (living, very weak suspension).—29,650, 21,300, 20,900, 19,000, 19,450, 17,950. *Neutrophils*—26.8, 53.4, 79.6, 59.1, 25.1, 24.2. *Lymphocytes*—67.8, 40.3, 15.8, 31.0, 69.2, 66.6. *Monocytes*—4.9, 5.9, 3.8, 8.8, 4.8, 8.7. *Eosinophils*—0.5, 0.4, 0.8, 1.1, 0.9, 0.5.

ENTRY OF ABDOMEN ONLY (0 and 4 hours only).—29,000, 17,750. *Neutrophils*—7.4, 30.7. *Lymphocytes*—85.7, 64.9. *Monocytes*—5.3, 2.9. *Eosinophils*—1.6, 1.5.

The graphs of granulocyte (neutrophil plus eosinophil) percentages for normal salt, staphylococcus, kieselgur and tubercle are:—

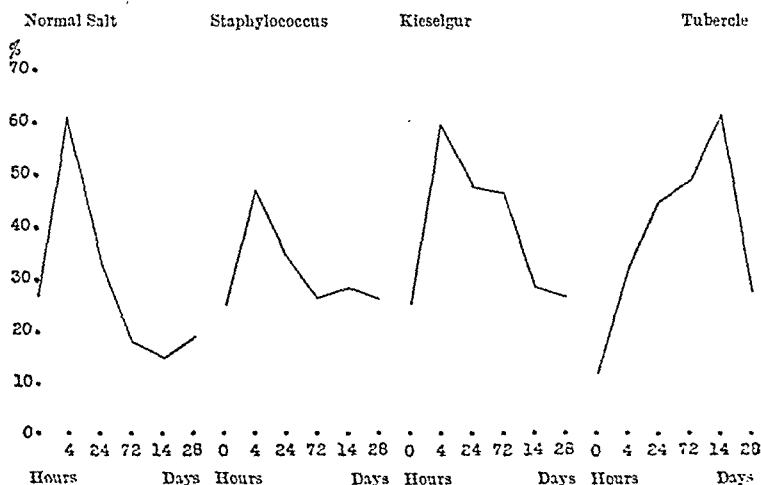


FIG. 4.—Granulocytes of Blood.

In this series, in which the blood reaction and not the tissue reaction has been investigated, we see once more that

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the sequence of cell-appearance is very much the same for all classes of irritant. There is nothing to point to a specific call by one irritant or by a group of irritants on one type of cell, nothing to point to the existence at the locus of irritation of a specific positive or negative chemiotaxis. Another phenomenon which becomes manifest in the peripheral blood-cell reaction is the leucopenia which has invariably followed these peripheral and intraperitoneal operations some time between the operation and an examination of the blood four hours later. In some cases the leucopenia was recovered from in twenty-four hours, in others it continued for some time, as in the instance of *B. tuberculosis*. In the case of *B. monocytogenes* it showed signs of progressive character right to the end of the time (twenty-eight days) allotted to the experiment. The leucopenia, moreover, also exhibited itself without any intraperitoneal injection of irritant, but with simple entry of the abdomen. That this again was not altogether a phenomenon associated with abdominal operation is indicated by the experiment in which the blood for examination was taken first from the extremity of the tail, no abdominal operation was performed, and then after an interval of four hours, blood was taken for examination from one foot instead of being taken again at the tail. The results here were: Leucocyte counts at 0 and at 4 hours respectively, 21,900 and 17,300; *Neutrophils*.—11.5, 14.7. *Lymphocytes*.—81.8, 76.8. *Monocytes*.—5.0, 7.8. *Eosinophils*.—1.7, 0.7 per cent. respectively. With a small animal like the mouse one has to keep in mind the possibility of shock even with a comparatively slight operation and there is reason to suppose that this is at least a partial explanation of the fall in leucocyte number, although the animals themselves gave no indication of suffering from shock, at all events with the simpler type of operation. In those cases where the irritant used was tissue destroying we might suppose that leucocytic destruction took place with production of a temporary leucopenia but this would not apply to a stimulus such as plain entry of the abdomen. It is more likely that we have here what Schilling¹⁸ calls a "distribution leucocytosis," a withdrawal perhaps of blood into dilated abdominal vessels, stasis and margination of certain types of blood cells. That this would lead to a temporary leucopenia in the peripheral blood is understandable and with the differentiation among leucocytes as regards the degree of their retention by adhesion to the walls of the dilated vessels we should expect,

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as we have obtained, an alteration in the relative or percentage count of cells. A simple hydræmia following on the traumata and irritation stimuli with which we are dealing could produce a leucopenia but would not account for the alterations which we have obtained in the differential leucocyte counts. Many observers, among others Shaw¹⁹ and Sabin, Cunningham, Doan and Kindwall²⁰ have pointed out that the erythrocyte curve does not follow the leucocyte curve in the physiological diurnal variations to which the latter are subject, but this might well be in accord with the explanation of abdominal vascular dilatation being the cause of withdrawal of cells from the peripheral circulation, if we assume that that withdrawal is to some extent selective for the different types of blood cell. We have ourselves, however, found anæmia as well as leucopenia to follow intraperitoneal injection, thus confirming the contention of Mole²¹ who found that in rabbits after operation involving the peritoneum there was a brief period of anæmia followed by polycythæmia. Our counts of peripheral blood erythrocytes in a mouse injected intraperitoneally with normal salt solution at 0, 4, 24, 72 hours, 14 days and 28 days were 8,816,000, 3,292,000, 6,400,000, 6,336,000, 10,092,000 and 6,224,000 per c.mm. respectively. But again we have to emphasise that our objective in this research was the determination whether specific cell reactions in blood and tissue followed the introduction of specific irritants into the tissues. That some such view is prevalent seems evident from the constant insistence on the operation of a force denominated positive and negative chemiotaxis, most of which dates from the epoch-making work of Metchnikoff.⁴ But that specific cell reaction to specific irritant is at the present time a current idea would seem to follow from such a remark as that, tuberculosis is "a disease which affects primarily a single strain of cells, namely, the monocytes" (Cunningham, Sabin, Sugiyama and Kindwall²²). All forms of tuberculosis, however, are evidently not characterised by monocyte increase in the blood and tissues. Gulland and Goodall²³ say of tuberculous meningitis that, "as distinguished from other forms of tuberculosis an increased leucocyte count is the rule. A count of 12,000 in the first week is very commonly met with. The increase is mainly due to polymorphs." Here we have an instance of an acute manifestation of an ordinarily chronic disease with a neutrophil percentage increase where examination has been carried out at an early stage in its evolution. Beattie,²⁴

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refers to a "preliminary polymorphonuclear leucocytosis which, in about two days, is followed by a great increase in the mononucleated cells," as the first of the series of events resulting from inoculation of tubercle into any tissue. Another disease for which it has become customary to regard monocytic increase of cells as having diagnostic value is malaria, or we might even say protozoal diseases generally. But, even in malaria, there are references to a polymorphonuclear cell reaction at some stage or other in the disease. Thus Ross and Thomson²⁸ say:—"We observed generally that the so-called polymorphonuclear leucocytes, though rather few during the pyrexial periods, do not vary much from day to day, but about seven days after the fever has abated their numbers are markedly increased. . . ." Schilling, with all his insistence on the importance of the hæmogram, is very careful to point out that its interpretation is only possible in as much as different pathological causes exercise different intensities of action upon the four groups of the blood elements, the erythrocytes, granulocytes, monocytes and lymphocytes. We might quote extensively to show that many workers have observed at different stages of one and the same disease a blood-cell picture which is at variance with what might be called its standard picture, but we do not wish to labour the point. In our experiments we have so far illustrated our theme of the sameness of cell reaction by applying the stimulus in the shape of one injection only of a sublethal dose. In the case of a disease we may imagine that, when it progresses, as it usually does for a time, we have the equivalent of the administration of multiple doses at varying intervals in its development. Our case is the simple one. In the other case the picture may be, and probably is, often confused. We have, however, done some experiments in imitation of the disease process and repeated the sublethal dose. We are reserving these experiments, which made little or no difference to the general thesis, for the next subject of our studies—the correspondence of blood picture with focal tissue picture in disease.

The meaning of our references to digestion leucocytosis, posture and exercise leucocytosis, etc., may not have been fully elaborated, but their relation to the subject matter of this article will be appreciated when we say that rather than speak of the diurnal leucocytic tides, as they have been called by Shaw¹⁹ being "independent of starvation, food, rest, exercise and sleep," we should regard these factors as representing

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stimuli or traumatisms, some one or other of which is always in action to account for the tidal rhythm observed in leucocytes during the 24-hour day. The effect may then be a purely non-specific one. The same argument of a purely traumatic influence seems to account for bone reaction, as well as blood or other tissue reaction. "Gravity," says Greig,¹² "is the great physiological trauma. . . . Changes in our habits, increase of adipose tissue, pregnancy, even the ingestion of food and a thousand and one things besides, which increase our weight or alter our bulk or posture call into action this insidious power." Workers in other directions than ours have stressed the non-specificity of causes of reaction, even when these, as is the case with bacteria, are supposed to be highly specific in character. Thoma held strongly by trauma as a universal cause of reaction. Friedberger²⁶ brought all the reactions to all pathogenic organisms down to one and the same "anaphylatoxin." Vaughan²⁷ had applied the idea to protein in general, and seemingly postulated a common toxic nucleus of the protein molecule. More recently still we have suggestions for a common causation of inflammatory phenomena, especially of the vasomotor type in the liberation of histamine. "Even the prick of a needle," says Findlay,²⁸ "causes a slight liberation of histamine-like substance." More directly in line with what we are contending for is the statement of Medlar and Kastlin,¹⁴ "Leucocytic response to damaged tissue is a general response regardless of whether the injury is produced by an infectious or non-infectious agent." It may be argued that the experimental results here presented are scarcely sufficient to bear the load of the generalised theorem of identity of the causation of tissue and blood reactions. This we recognise to the full, but we submit, as further justification of the thesis, that our study in the course of routine examinations of pathological skin conditions, which are very pertinent to this enquiry, has impressed us with the sameness of reactions for very variously named conditions. The papule, the vesicle, the pustule and the plaque, the granuloma and the subcutaneous abscess, the subepithelial and deeper lymphocytic infiltrations seem to represent, all of them, phases of reaction to the one cause, trauma. In the language employed by some of the earlier workers who resisted Metchnikoff's claims, we are averse from crediting the polymorph with perspicacity or the monocyte with defence decisions. The advent of leucocytes or other

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wandering cells at the *locus læsionis* may be more a matter of accident than of attraction.

To summarise. Under the conditions of our limited experimentation, we feel disposed to think that:—

1. There is an invariable sequence of events in response to the introduction of foreign material into the body, a polymorph infiltration followed by a monocytic and, if time allows, a lymphocytic.

2. The lymphocyte, monocyte, macrophage and giant cell probably represent stages of development of one and the same type of cell.

3. No matter what the nature of the stimuli—trauma; injection of salt solution, indian ink, staphylococci, tubercle bacilli or benzole; ingestion of food or fluid; posture; application of heat; muscular exercise—they all produce the same sequence of events so far as cell response in the tissues or in the blood is concerned.

4. There is not yet sufficiently conclusive evidence, except by extension of the local influence and of deficiency of cells, for chemical action at a distance as a factor in production of blood and tissue cell response. Vasomotor and sympathetic nerve stimulation, which produce distant effects, are of the nature of propagated nerve stimuli. One may speak of a positive chemiotaxis in the sense of collection of cells to a focus but not in the sense of a specific call for a special type of cell. It is doubtful whether negative chemiotaxis exists at all.

5. The special tissue manifestations and blood pictures attached to particular diseases and assisting in their diagnosis are reducible to manifestations of simple acuteness or chronicity, local tissue destruction, and duration of stimulus, thus making the blood picture especially a matter merely of the time at which the examination is made. There is nothing specific about the cellular reaction in disease, or in physiological states. There is only variation in the degree and duration of a phase.

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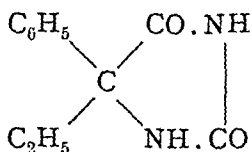
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(To be continued.)

THE TREATMENT OF CHOREA BY NIRVANOL.

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SINCE the introduction of nirvanol in the treatment of chorea by Roeder,¹ in 1919, this method has been extensively used chiefly in Germany. Nirvanol, whose chemical name is *aa*-phenyl-ethylhydantoin, has the formula:—



The drug contains hydantoin, a chemical group which is not used in any other form in pharmacology and whose action is unknown. It is thought that this chemical group is the active part of the compound and is responsible for its action. Nirvanol is most nearly allied to the barbituric acid group of hypnotics, and was first used as a hypnotic and sedative before its use in chorea was discovered.

In most cases a nirvanol reaction is produced after the daily oral administration of 0.3 gram for a period of from eight to fourteen days. The patient develops a morbilliform rash usually on the chest, abdomen and limbs, the face being only slightly affected, though some œdema of the eyelids and conjunctivitis may occur. A rise of temperature is usually reported to occur and last a few days, and this may be as high as 104° F. in some cases; with the pyrexia there is a corresponding increase in pulse-rate. In the majority of cases before the onset of the reaction the choreic movements are aggravated but show a very marked improvement with the disappearance of the rash, which leaves no trace behind and is not followed by desquamation. Practically all the observers have reported favourably on the effectiveness of the drug in chorea, but many consider that its use is not justifiable in a self-curable disease, on account of the severe and dangerous reactions which may result and which are not predictable or preventable. The present paper reports the effects of nirvanol administration to 15 patients, and compares the results with those obtained by more conservative measures on 15 cases of chorea.

The Treatment of Chorea by Nirvanol

Clinical Material.—The 15 nirvanol treated cases are divided into two groups. Group A. comprises the 10 cases which developed a typical nirvanol reaction with a rash (Table I.). Table II. shows the 5 cases in whom no rash was obtained. Of these 15 cases receiving nirvanol, 13 suffered from moderately severe chorea, concerning the diagnosis of which there was no doubt. Case No. 4971 in Group A. was probably not a case of true chorea, but showed choreiform movements superimposed on a spastic paralysis resulting from a birth injury. In this case no rheumatic history could be obtained and no rheumatic manifestations were discovered. Case No. 4911 in Group B. was primarily a case of asthma in a highly neurotic woman who had shown choreiform movements intermittently since early childhood. She also showed no signs of rheumatic infection and gave no suggestive history. These were the only two cases not benefited by nirvanol.

The 15 control cases suffered from chorea of a severity similar to those getting nirvanol. As can be seen from the tables the average ages of those developing a nirvanol rash and those acting as controls were practically identical.

Dosage.—The same dosage of nirvanol was employed in all cases except one (4808) in which an idiosyncrasy to the drug was found. The drug was given orally in doses of 0.3 gram once daily until a rash appeared, or for twelve to thirteen days if no rash developed. This is the dosage most commonly followed,^{2, 3, 4, 5, 6, 7, 8} though some observers have given much bigger doses without any ill effects.^{9, 12}

From Tables I. and II. it can be seen that, whereas those developing a rash received an average total of 3.33 grams of nirvanol, and those not showing a rash, 3.54 grams, these latter were given considerably less per lb. body weight. The former group received 0.045 gram per lb. and the latter 0.033 gram—a difference of 35 per cent. On working out similar figures for the cases treated by East and Cullinan,⁸ it was found that the average dose given to those developing a rash was 0.042 gram per lb., and that those not developing a rash received 0.034 gram per lb.—a less marked but similar difference.

Rash.—In nine cases the rash was of the morbilliform type usually described, whilst the other patient showed a scarlatini-form eruption. The rash appeared usually on the tenth or eleventh day of treatment, the outside limits being the ninth and eighteenth days. In two cases the rash did not appear until after the nirvanol administration had been stopped for

TABLE I.
10 *Nirvanol* Cases Developing Rash.

Case Number.	Sex.	Age.	Attack.	Weight in lbs.	Total grms. of Nirvanol.	Grms. per lb.	Day of Rash's Appearance.	Temperature.	Total Days in Hospital.		Days after Nirvanol.	Remarks.	Result.
4543	F	8	2nd	51	3.3	0.065	11	99°	21	10	10	Mitral incompetence	V.M.I. Cure
4829	F	17	1st	110	3.9	0.035	13	...	28	13	13	Mitral stenosis and incompetence	"
4858	M	11	1st	72	3.0	0.042	10	...	20	10	10	Rash 2 days after nirvanol stopped. Spastic paralysis. ? True chorea	No improvement
4971	M	12	?	72	3.6	0.050	14	102°	63	54	54	...	Cure
5106	F	12	1st	69	3.3	0.048	11	...	24	11	11	Rash scarlatiniform	"
5153	F	10	1st	74	3.0	0.041	10	...	19	7	7	Kept in hospital after movements ceased, to improve general nutrition	V.M.I. Cure
4921	M	11	1st	56	3.0	0.054	10	...	50	35	35	...	"
5239	F	16	1st	98	3.3	0.034	0.034	11	...	23	13	11 doses, 2 days' rest, then 3 more doses, and 2 days later, rash	"
5516	F	12	1st	79	2.7	0.034	0.034	9	...	28	15
5551	F	13	3rd	66	4.2	0.061	0.061	18	...	28	6
Average				74.7	3.33	0.045	0.045	11.7	...	31.4	15.4

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TABLE II.
5 Nirvanol Cases not Developing any Rash.

Case Number.	Sex.	Age.	Attack.	Weight in lbs.	Grms. of Nirvanol.	Grms. per lb.	Temperature.	Total Days in Hospital.	Days after Nirvanol.	Remarks.	Result.
4685	F.	19	2nd	133	3.6	0.027	...	18	3	...	Cure
4808	F.	10	2nd	58	2.7	0.047	100°	36	5	Idiosyncrasy to nirvanol	"
4911	F.	30	?	111	3.6	0.032	...	32	13	Asthmatic. ? chorea	No improvement
5126	M	18	1st	133	3.9	0.029	...	54	18	Nirvanol after failure with preliminary course of arsenic. Mitral stenosis	Cure
5146	M	13	1st	99	3.9	0.039	...	36	19	Kept in hospital for teeth extraction and general nutrition. Mitral incompetence	"
Average	{ F 3 M 2 }	18.2	{ 1st 2 2nd 2 }	107	3.54	0.033	...	35.2	11.6

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some days. In no case was there a secondary reaction, though this has been described as occurring days or weeks after the original reaction.^{8, 10, 11}

Temperature and Pulse.—In only three cases was there any febrile reaction, and the maximum temperature recorded was only 102° F. Similarly an increase in pulse-rate was only found on four occasions. These findings are unusual, as most observers have reported a much higher incidence of febrile disturbance, lasting often for days, either with or without a rash.^{2, 3, 4, 7, 8, 12} In Ashby's series of 12 cases, however, only one patient showed a rise of temperature, and there was no increase of pulse-rate.¹³

Blood Changes.—The administration of nirvanol is always accompanied by changes in the blood picture, and leucopenia and eosinophilia are constantly reported to occur even in the absence of other signs of a reaction. In this series regular blood examinations were not carried out, but when films were examined an eosinophilia was always found—a maximum of 11 per cent. being recorded in one patient. The leucopenia found is due to depression of bone-marrow function, and is considered by Goebel⁶ to be one of the more serious manifestations of nirvanol intoxication.

Idiosyncrasy.—Case 4808, F. 10. Nirvanol was started in doses of 0.3 gram daily, but after the second dose the child's face became puffy and there was marked œdema of the upper lip with general malaise and a temperature of 99° F. This subsided in two days, and after four more days the same dosage was restarted. After two doses there was again general malaise and a rise of temperature to 100° F., and the nirvanol was discontinued, although no other signs were present. A mild pyrexia and increase of pulse-rate continued for four days, and swelling of the face and especially of the lip again made their appearance two days after the drug was discontinued. The swelling subsided in two days and minimal doses of nirvanol were recommenced. The patient was given 0.075 gram daily for seven days, and then the dose was doubled and continued for a further week, when, as all movements had ceased, the nirvanol was stopped. A similar reaction associated with a rash has been reported by Lesingang¹⁴ after a single dose of the drug. Four of this series of cases had definite cardiac lesions, and the treatment appeared to have no adverse effect, which is borne out by other reports.^{2, 8}

Results.—Of the nine cases of chorea developing a rash

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TABLE III.
15 Cases not treated by Nirvanol.

Case Number.	Sex.	Age.	Attack.	Weight in lbs.	Treatment.	Total Days in Hospital.	Remarks.	Result.
3170	F	15	1st	113	Screening. Liq. arsenicalis	70	Mitral incompetence	Cure
3171	F	12	1st	52	R.I.B.	34	...	"
3454	F	6	1st	46	R.I.B. Aspirin	40	Mitral incompetence and aortic stenosis	"
3581	F	7	1st	39	R.I.B.	46	Mitral incompetence	"
3659	F	15	4th	94	R.I.B. Salicylates. Tonics	81	Temperature and pulse sub-acute rheumatism. Mitral incompetence	"
3724	F	13	2nd	74	R.I.B. Antipyrin. Tonics	36	Mitral incompetence	V.M.I.
3908	F	9	1st	56	R.I.B.	37	...	Cure
3969	M	15	1st	88	Liq. arsenicalis. R.I.B.	59	...	"
4026	F	12	1st	70	R.I.B. Salicylates. Liq. arsenicalis	68	No response to salicylates. Improvement coincident with arsenic	"
4132	F	16	1st	72	R.I.B. Chlor. and brom. Liq. arsenicalis	56	Very marked case, thought at first to be encephalitis. Mitral incompetence. Rheumatic nodules	"
4169	M	15	3rd	113	R.I.B.	21	Mitral incompetence	V.M.I.
4236	M	13	4th	68	R.I.B. Liq. arsenicalis	36	"	"
4360	F	12	2nd	78	"	20	"	"
4469	F	14	4th	118	R.I.B.	24	"	"
5090	M	8	1st	50	R.I.B. Tonics	70	Had tonsils and adenoids removed	Cure
Average	{ F 11 M 4 }	12.1	{ 1st 9 2nd 2 3rd 1 4th 3 }	75.4	...	46.5

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seven were completely clear of choreic movements on discharge and the remaining two were greatly improved. In the other group of four cases of true chorea not showing a rash all showed complete disappearance of symptoms. In the control series of 15 cases, 11 were free of movements and 4 greatly improved on discharge. The improvement seen in the cases in Group B. is of interest. Some observers have only found benefit to follow on the production of a typical reaction, but quite a large number of cases have been reported as showing improvement when the patients have remained afebrile throughout.^{2, 8, 16}

On comparing the duration of hospitalisation a significant difference is found between the controls and the nirvanol-treated series. In Group A. the average total time spent in hospital was 31.4 days and in Group B. 35.2 days. These figures would be considerably improved by the omission of the case of spastic paralysis, and if it is taken into account that one case had a preliminary unsuccessful course of treatment with Fowler's solution. If these two cases are excluded the figures for Groups A. and B. become 27.3 days and 30.5 days respectively, and the duration of treatment was thus 16 to 19 days less than the average of 46.5 days spent in hospital by the control cases. These results are in agreement with several other published figures.^{2, 9, 16} Goebel's figures were 24 to 25 days' treatment as compared with 43 to 51 days in those treated by other measures.

Discussion.—It would appear as possible that one of the reasons for the non-development of a rash in certain cases is the smallness of the dosage. It has been shown that these cases received less nirvanol per lb. body weight, and the possibility is strengthened by the fact that similar figures were obtained from another series of cases. That this is, however, only one factor is seen from the occurrence of reactions after very small doses in some cases. At present, the mode of action of the drug is quite unknown, in spite of extensive animal experimentation in Germany.

Owing to the possibility of idiosyncrasy and the development of alarming reactions, it is not considered advisable to use the drug except under close supervision. In hospital it appears to be useful in cutting down the duration of treatment necessary for the disappearance of symptoms. It could be suggested from the figures obtained in this series that the drug should be administered in doses of 0.3 gram daily either until a reaction

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is produced or until about 0.045 gram per lb. body weight (0.099 gram per kilo) has been given, rather than for an arbitrary period of time. Sufficient time has not elapsed, and a large enough series has not been treated for the late results of treatment to be analysed, and the incidence of relapses and conditions compared with that usually found. One of the present series has been subsequently readmitted owing to reappearance of choreic movements and similar relapses have been reported.

Summary.—1. Fifteen cases have been treated by nirvanol with satisfactory results.

2. The duration of treatment is appreciably less than that required for control cases.

3. One case of idiosyncrasy was encountered.

4. A method of dosage is suggested.

My thanks are due to Professor Murray Lyon for permission to publish these results.

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THE RELATION OF HYPERFUNCTION OF THE POSTERIOR LOBE OF THE HYPOPHYSIS TO ECLAMPSIA AND NEPHROPATHY OF PREGNANCY.

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Department of Physiology, Edinburgh University.)*

THE view that the various toxæmias of pregnancy result from a common etiological factor has been expressed several times; and, struck by the importance of this conception, we sought for such a common basis which would account for the characteristic clinical symptoms of toxic albuminuria of pregnancy and of eclampsia, namely, the water retention and œdema associated with inhibition of diuresis, the capillary spasm, and the rise in blood-pressure. The purpose of this communication is to show that hyperfunction of the posterior lobe of the pituitary gland affords a consistent explanation of these phenomena, and that such excessive activity can in fact, be demonstrated. We have devised a method by which the antidiuretic component of the posterior hypophysis can be recognised in the blood, and have isolated a vasopressor substance which is apparently identical with the pressor autacoid of this gland.

Our method of demonstrating pituitary hormone in the blood derives from the fact that the presence of protein weakens its activity and that it is destroyed by even a slight degree of alkalinity. Trendelenburg, for example, found the effect on the melanophore cells of amphibians of pituitrin in serum was much less than that of a similar quantity in saline, while M'Cord observed that the addition of blood to pituitary extracts abolished the pressor action. Dudley, Abel, Guggenheim and others, proved this hormone to be so exceedingly alkali labile that this property serves to distinguish it clearly from similar substances. The attempt to separate the hormone from serum protein at a weak acid reaction gave the best prospect of success, since near the isoelectric point of the protein a minimum of free valence is exhibited, and the union with the hormone is at its lowest.

About 40 c.c. of venous blood is collected, coagulation being prevented by the addition of 2.0 c.c. 5 per cent. sodium citrate,

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centrifuged, and 1 c.c. normal acetic acid added to 20 c.c. plasma. This brings the plasma reaction to pH 3.9 to 4.3 as measured by the hydrogen electrode. It is then filtered under a negative pressure through a filter of acetic colodion till about two-thirds of the amount pass through. The ultra-filtrate having been proved to be protein-free, is kept on ice till it is used, which should be done as soon as possible. Immediately prior to the experiment the acid ultra-filtrate is carefully neutralised by the addition of normal sodium hydroxide.

Since Van de Velde's discovery that injection of posterior pituitary extract in man led to a long-continued inhibition of diuresis, this property of the hormone has been widely studied both clinically and experimentally. If a large quantity of water is administered to an unnarcotised animal by means of a stomach-tube and simultaneously pituitary extract is injected subcutaneously, the urinary excretion sinks greatly for some hours, even to the point of anuria. When the effect wears off considerable diuresis occurs. During the period of inhibition the chloride content of the urine rises considerably even to such a point that the absolute quantity excreted is above normal in spite of the diminished urinary output (Fromherz *et al*). As Starling and Verney and Poulsson have shown, the effect is produced in the first instance in the kidney where the water reabsorption is increased, in the second to an extrarenal field whereby there is a fluid displacement between the blood and the tissues.

The method of Kestranek, Molitor, and Pick was adapted to the evaluation of the antidiuretic activity of the blood extract. Fasting rabbits received 90 c.c. water by stomach-tube and a subcutaneous injection of 10 c.c. of ultra filtrate, or in the case of the controls, 10 c.c. of a physiological saline plus a suitable addition of a neutral acetic acetate mixture. The urine was obtained from the animals at half-hour intervals by pressing the bladder, and the chloride content of each sample analysed. The normal excretion curve of a rabbit treated in this manner is subject to certain variations in part dependent on careful feeding and environment; but even when these factors were properly adjusted about half the rabbits used in over 200 diuresis experiments proved unsuitable and were discarded. From the remainder graphs varying within narrow limits were readily obtained, with a characteristic shape showing the increase of urinary excretion up to the third or fourth half-hour

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period. The normal curve was determined by at least three control experiments and this was retested from time to time. Corresponding experiments were always done on the same

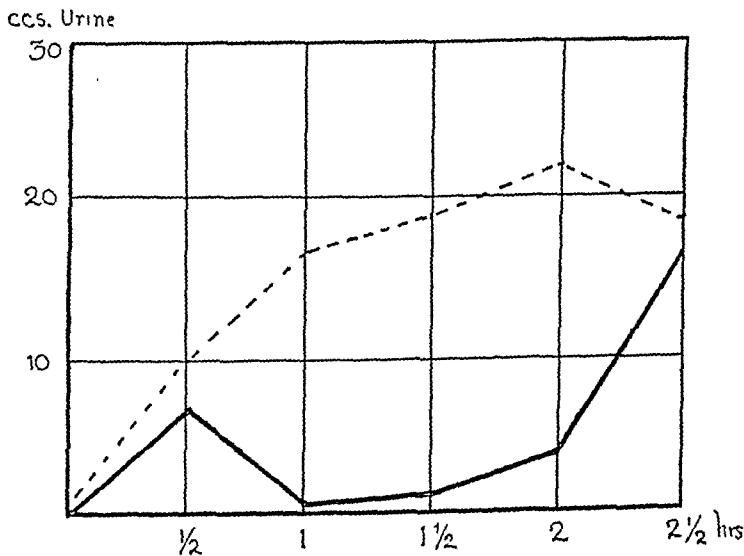
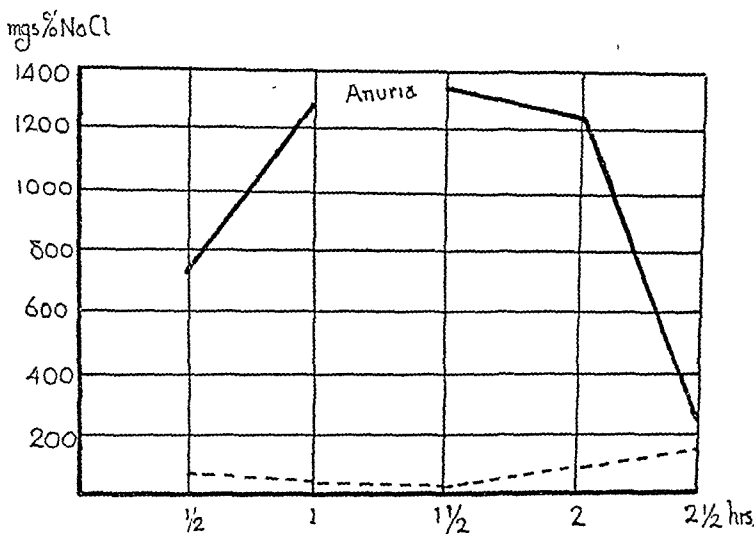


FIG. 1.

animals as the form of the excretion curve varies in different rabbits, and indeed it was found most satisfactory to carry out the bulk of the experiments on the smallest possible number of standardised animals.

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Figure 1 shows the normal diuresis of a rabbit with the sodium chloride content of each half hourly sample, and plotted on the same graphs are the volume and chloride

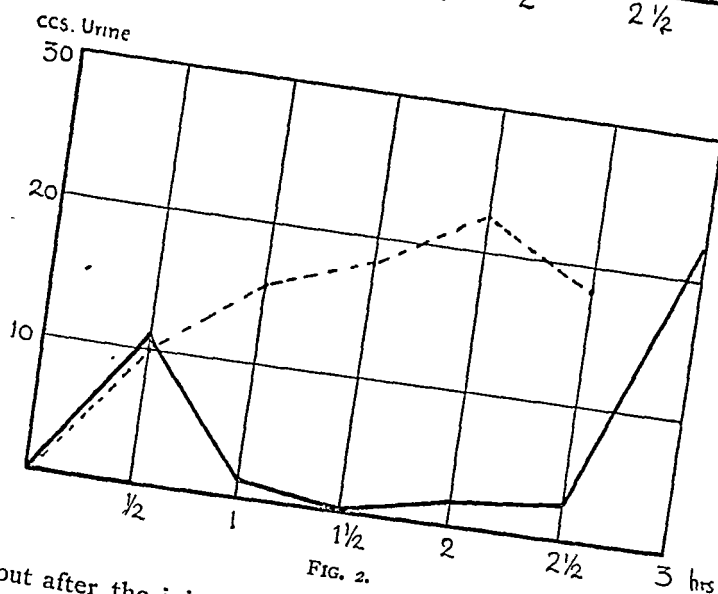
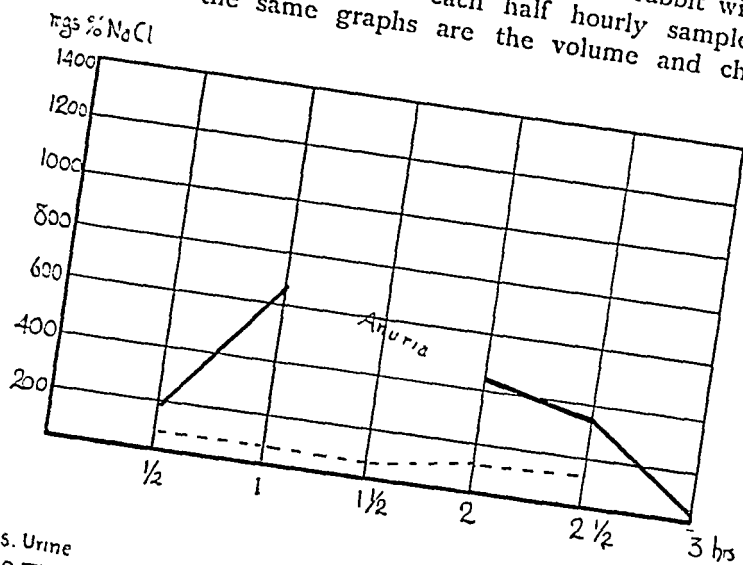


FIG. 2.

output after the injection of 0.15 pituitan (Henning) showing so strong an effect that the animal is almost anuric in the third half hour, and it is only after the fourth half hour that the inhibition is removed. From the upper diagram it will be seen

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that urine excreted under the activity of pituitrin is characterised by a high chloride content, this reached 1375 mgrm. per 100 c.c., while in the control experiment the amount was not higher than 140 mgrm. per 100 c.c.



Similar inhibition of diuresis is obtained if, in place of pituitary extract, one injects 10 c.c. of an ultra-filtrate from the blood of patients with toxic albuminuria of pregnancy or eclampsia, and this is shown by Fig. 2. The same rabbit was used as in the first experiment, and 10 cc. of an ultra-filtrate of blood from a pre-eclamptic was administered. The activity of the ultra-filtrate on the urinary excretion is similar to that of the glandular preparation. After an hour and a half, anuria occurs, and after the fifth half-hour sample, the inhibition rapidly diminished; the chloride content bears the same relationship as in the pituitary experiment.


Similar curves to these were obtained from all of twenty-four cases of toxic albuminuria and eclampsia which showed œdema clinically. Only in one case of eclampsia was no anti-diuretic principle demonstrable, and in this case œdema was absent. Control tests on healthy, pregnant, and non-pregnant women, were entirely negative, with one exception. In this case the woman had aborted a fortnight previously, but was otherwise healthy, and a positive antidiuretic effect was produced by her blood filtrate on two animals. She had to be dismissed from Hospital, and it was not possible to follow her case further.


We do not know of any substance possibly occurring in blood other than pituitary hormone which possesses this characteristic pharmacological activity, but to establish more firmly the identity of the antidiuretic component in the blood of these patients with that of the pituitary, other properties have been examined. The pituitary hormone is destroyed by weak alkali, and by ultra-violet irradiation, and is absorbed by talc. Ultra-filtrates of known antidiuretic potency were therefore made alkaline, or exposed to a mercury vapour lamp for an hour, or shaken with talc. All these procedures removed the inhibitory effect on urinary excretion, and concurrently the influence of the chloride content of the urine. The agreement in physical and chemical properties thus confirms the identity.


One of the first recognised properties of pituitrin is its production of peripheral vasoconstriction and increased blood pressure. Since a pressor effect determined by capillary spasm


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is a symptom commonly associated with nephropathy and eclampsia, the reproduction of this in animals by the ultra-filtrates possessed a double significance for us in further establishing the identity of the active substance as pituitrin and in substantiating the hypothesis for the cause of the symptoms. The pressor activity of the ultra-filtrates was tested by the non-fatal method of Koch and Meis on unanæsthetised animals and also by means of the usual fatal experiment method. Figure 3 shows the action of 12 c.c. of an ultra-filtrate from a nephropathic patient whose blood-pressure was 230 mm. Hg, on a rabbit. The increase is obvious, and in this experiment reached a maximum of 26 mm. 35 minutes after the injection.

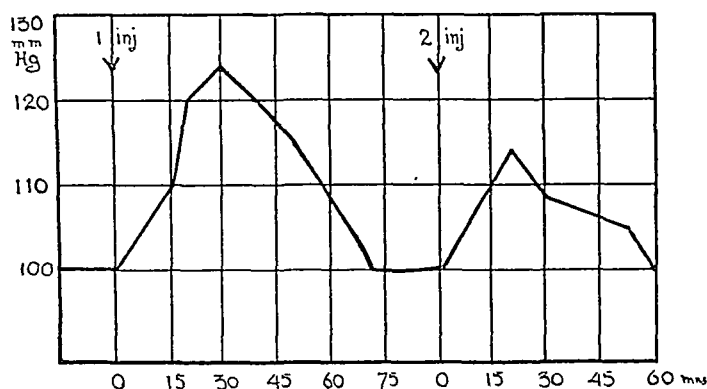


FIG. 3.

A characteristic of the pressor component of the posterior pituitary gland is that a second similar injection given after the effect of the first has passed off, is much weaker. This is also shown in the figure.

The pressor substance was recognisable in 10-12 c.c. of all cases of nephropathy and eclampsia in which the B.P. of the patient reached 180 mm. Hg. Even with double the quantity of ultra-filtrate obtained from healthy pregnant and non-pregnant women, no pressor influence was obtained. Just as in the case of the antidiuretic component the active substance was found to be alkali labile, destroyed by irradiation with ultra-violet rays, and to be absorbed by talc, thus agreeing with the chemical and physical properties of the glandular preparation. One difference was found, however; the pressor activity is only displayed by glandular extracts when injected intra-

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venously, being almost inactive hypodermically, while the blood filtrate proved to be active when injected under the skin. This difference is not an important one, and an analogy to it is found in the case of the thyroid; this autacoid naturally occurring in the blood is also more biologically active than glandular preparations. While the vasopressor component of the ultra-filtrates is probably identical with that of the pituitary, strict proof cannot yet be adduced.

Another effect of the pressor principle of the pituitary is to expand the melanophores in the frog's skin. This was also demonstrated in ultra-filtrates in all of a small number of our series of patients. Only a few cases were tested as the ultra-filtrates were required for the other tests, and further this experiment did not appear to throw any further light on the clinical aspects of the problem.

Turning again to the patients, we are at once reminded of the importance of the endocrine system in pregnancy: it is indeed no exaggeration to say that the action of pregnancy on the maternal organism can be considered almost exclusively as an endocrine problem. The increased autacoid function of the ovary and anterior pituitary lobe during pregnancy is generally known, but in addition heightened activity is recognisable in other ductless glands which do not stand in such direct relationship to the reproductive system. This is specially true of the thyroid, for thyroxin is recognisable in greatly increased quantity in the blood during healthy pregnancy (Anselmino and Hoffmann, Eufinger *et al*) and is the cause of a series of deviations in metabolism, in circulation, and in nervous excitability by which the healthy pregnant woman differs from the non-pregnant. Apparently there is also increased function of other endocrine organs, the pancreas, adrenals and posterior pituitary. In short, normal pregnancy produces a condition of hyperactivity throughout the system of ductless glands, but in contra-distinction to endocrinopathies a harmonious balance is still maintained thus securing the regulated course of life processes with objective and subjective well-being of the woman.

The pituitary source of the pregnancy toxicoses, nephropathy and eclampsia, was first suggested by Hoffbauer and later by Rossenbeck and by Kustner, but as it was not possible to adduce experimental proof, the contentions of these workers were not widely discussed. The most important clinical

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aspects mentioned by these authors, and arising from our own observations now require consideration.

For the last thirty years research has been chiefly directed to a search for the toxin of the worst form of the toxicoses, namely eclampsia, and especially for an agent which could produce the fits, but we preferred to study the less severe cases with a view to elucidating the metabolic disturbances on which the toxicoses depend. Coma and fits are not specific appearances, but are repeatedly found in many other types of disease, and their dramatic character only serves to overshadow the underlying metabolic disturbance which is best exemplified in pre-eclamptic states, *i.e.* in patients with dropsy and nephropathy.

The main metabolic upset in such cases is the tendency to water retention as Zangemeister showed; and he further demonstrated that the disturbance in water economy is not caused by disease of the kidney but in fact precedes it. This disease of the kidney is indeed the sequel of water retention or of the toxin which is responsible for the retention.

When the pregnancy toxicoses are included (at first only hypothetically) among endocrine disorders it is at once recalled that the cardinal symptom of water retention can be duplicated by the characteristic pharmacological action of the posterior hypophyseal autacoid which acts apparently by causing increased absorption in the tubules. (Up to the present it is not possible to say whether long continued administration of pituitrin will reproduce the morbid histology of nephropathy in animals. Chronic pituitrin poisoning of rabbits gave a typical picture with cloudy swelling and fatty degeneration of the tubules, and some glomerular change. The rabbit is not satisfactory material as we found alterations in a similar direction to the above in a few of a control series of healthy animals. This experiment will be repeated with more suitable animals.)

The second feature of the toxicoses that springs to mind is the very frequent rise in blood-pressure and this too corresponds with the vasopressor component of pituitrin.

On comparing the other important clinical features of nephropathy and eclampsia with the actions of the posterior pituitary autacoids, further agreement is found. Rowntree produced coma and fits in rabbits by combined pituitrin and water poisoning, which appear to have been much like eclampsia. Lung œdema is a characteristic post-mortem

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appearance in eclampsia and (quoting from Trendelenburg) animals poisoned by large doses of pituitrin show marked œdema of the lungs.

Seitz and also von Spiegler and Scholl showed that in these toxicoses there was a reduction of the nerve-muscle excitability to galvanic current, and according to Eddy and to Yoshimoto a like diminution is shown by animals under the influence of posterior pituitary.

Again von Rossenbeck describes a shift of sodium from the blood into the tissues in pregnancy toxicoses and the similar redistribution was demonstrated experimentally in animals by Gollwitzer-Meyer. It has also been shown that there is a diminution of blood calcium in eclampsia, and we have been able to reproduce this with pitressin, and to a lesser extent with pitocin.

The tendency to capillary spasm in the toxicoses was emphasised by Hinselmann and others, and of course the contractile action of pituitary hormone on the capillaries is well known.

An interesting observation of von Molitor and Pick, and others is, that the effect of the posterior pituitary is lessened by certain, but not all, narcotics and hypnotics, and these happen to be the same drugs which are employed quite empirically in the Stroganoff treatment of eclampsia.

All these considerations make it appear more probable that nephropathy and eclampsia are caused by increased posterior hypophyseal function.

Not only have we been able to detect an increased content of posterior pituitary hormones in the blood of all our cases, but it has been possible to demonstrate a relationship between the amount present and the severity of the symptoms. Twenty-five cases have been investigated, eleven of eclampsia and fourteen of nephropathy, and repeated estimations were made in most, either for control of the first experiments, or for identification of the active substance. As far as possible quantitative hormone estimations were carried through, and in nephropathy the influence of therapeutic treatment followed, or the influence of birth and the puerperium on the hormone content studied.

The antidiuretic principle was present in all cases in which œdema occurred, *i.e.* in 24 out of 25 patients. The exception was a pre-eclamptic in whom the blood-pressure was raised,

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but showed no œdema, and here the antidiuretic component was absent.

The quantitative estimation was followed out by comparing the blood ultra-filtrate activity on diuresis inhibition with a known commercial standard (Pituigan, Henning). In cases with considerable œdema a content of 5 to 8 Voegtlin units per litre plasma was present, and in slighter cases from 2 to 3 units. These figures have however, only a nominal value since it is not known how much of the active substance is lost by absorption or otherwise during the preparation. The hormone content appears to run parallel with the severity of the symptoms, and as these abate so is the amount lessened. So far, our experience is that in eclampsia the content of antidiuretic substance is not higher, indeed it is often lower than in severe toxic albuminuria of pregnancy.

Labour exerts a decisive influence on the amount of circulating antidiuretic substance; especially in eclamptics twenty to thirty hours after labour there is none, or only the least recognisable quantity. Concurrently the attacks cease. In the only case of puerperal eclampsia available there were large quantities of the antidiuretic substance in the blood.

The pressor substance was recognisable in all cases in which the blood-pressure exceeded 180 mm. Hg. Among these was the pre-eclamptic mentioned above who showed no œdema. Her pressure was 225 mm. Hg. and her blood filtrate raised that of a rabbit from 125 to 135 mm. Hg.

It must now be asked whether the endocrine disturbance is limited to the hypophysis, for the thyroid is in many ways a physiological antagonist to it. Thyroxin stimulates diuresis, posterior pituitary inhibits it; thyroxin increases galvanic excitability, and is a vasodilator, pituitrin diminishes it and is a vasoconstrictor. By a method lately described by two of us (Anselmino and Hoffmann), we have estimated quantitatively the amount of thyroid hormone in the blood. In non-pregnant women the content is below the threshold of our method, but in healthy pregnant women the amount is so increased that exact quantitative evaluation is possible. The consistent and regular results of these estimations show that in nephropathies the thyroid content is mostly lower than in normal pregnancy, but in eclampsia there is a moderate increase above the normal values of pregnancy, although it is sometimes not more than about the upper limit of normal variation. It would appear

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that the disturbance of internal secretion in the toxicoses is not limited to the hypophyses, but that the thyroid is also involved. Thus while an uncompensated over-activity of the posterior lobe of the pituitary is the most prominent feature of the toxicoses, they must be regarded as pluriglandular symptom complexes. Different participation of the other glands would account for the demarcation between nephropathy and eclampsia, and this is possibly also due in some measure to differential production of the two or more hormones of the posterior pituitary.

The mechanism by which the pathological picture is produced expands Zangemeister's teaching and may be briefly recapitulated. In toxic albuminuria a slowly increasing production of antidiuretic substance associated with a lessened production of thyroxin, is followed by water retention and inhibition of diuresis. The site of action is in the kidney tubules and there one finds the damage preponderatingly localised, but this, it must be remembered, is a sequel to the water retention and rapidly disappears as soon as the inhibition is removed. This explains the striking phenomenon of the great diuresis, often several litres daily, which occurs shortly after labour. The extreme suddenness of onset suggests that coincident with labour a causal mechanism for the inhibition is removed. The frequently recognisable vessel changes may in part be determined by the associated increase in pressor substance.

In eclampsia the onset is usually sudden, though the disease is often preceded by toxic conditions early in pregnancy, and frequently occurs about, or not long before labour. It is associated with a sudden increase in the circulation of antidiuretic substance and also of the pressor principle, and we may recall that sudden increase of the posterior pituitary autacoid has been adduced in several quarters as the cause of the onset of labour. The antidiuretic action produces an acute disturbance of water economy and of ionic distribution in the body fluids, and this leads to œdema of the brain, or in Zangemeister's sense to brain pressure, with resultant cerebral irritation, fits and coma. Simultaneously kidney changes in the direction of nephritis are produced. In the second place we may follow Volhard, and suggest rather that the increase in pressor substance leads to the onset of the eclamptic attack through vasoconstriction to brain irritation and fits. The displacement of blood into the lung vessels and splanchnic area may well

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be contributory to the occurrence of lung œdema, and the occasional appearance of portal thrombosis. How far each or both of these mechanisms are responsible and how far other endocrine components are involved must still be left open for the complexity of the eclamptic picture excludes a completely schematic etiology.

The problem of liver damage has not been alluded to for its exact bearing is not yet clear, and it is being investigated further. One need only be reminded that the toxicoses are essentially metabolic disorders, and thus almost *a priori* the liver is involved. Further, the hypothesis is not upset in any way by the pathological changes in this organ.

Conclusion. — The excessive presence of antidiuretic and pressor principles in the blood of patients with toxic albuminuria of pregnancy or eclampsia has been demonstrated, and their chemical and physical properties found to be identical with those of the autacoid of the posterior lobe of the pituitary gland. Full agreement was established between the most important individual symptoms and experimentally reproducible actions of the autacoid; these included water retention through diuresis inhibition, rise in blood-pressure, capillary spasm, coma and fits, lung œdema, the lessening of galvanic irritability, certain ionic movements from blood to tissues, and the controlling effect obtained by certain definite narcotics and hypnotics. Quantitative estimations of the autacoid ran parallel to the severity of the symptoms. The hypothesis is advanced that toxic albuminuria of pregnancy and eclampsia are endocrine disturbances probably of a pluriglandular nature, but in which great over-production of the hormones of the posterior pituitary dominates the picture.

Since the above was written our attention has been drawn to a recent paper by M'Quarrie and Peeler entitled "The Effects of Sustained Pituitary Antidiuresis and Forced Water Drinking in Epileptic Children" which affords additional support to our hypothesis. These workers show that typical *grand mal* seizures can be induced within 12 to 48 hours in the epileptic but not in the non-epileptic subject by giving water at the rate of 2 to 5 c.c./kilo body weight per hour while maintaining effective antidiuresis by means of pituitary extract. Under the conditions of the experiment dilution of extracellular body fluids appears to be an essential factor in the

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induction of seizures, since administration of sodium chloride in amounts just sufficient to prevent this tends to interfere with their occurrence. The authors are of the opinion that these results tend to show that the mechanism for controlling the semi-permeability of the brain-cell membranes is inherently defective in the epileptic patient.

This investigation was carried out during the tenure by one of us (W. P. K.) of a Beit Memorial Fellowship for Medical Research.

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A PRELIMINARY NOTE UPON THE OCCURRENCE OF INCOMPLETE DEVELOPMENT OF THE STRIATED MUSCLE FIBRE AS A CAUSE OF CERTAIN CONGENITAL DEFORMITIES OF THE EXTREMITIES.

By D. STEWART MIDDLETON, F.R.C.S.

THE unsatisfactory nature of the current theories that are held to account for congenital distortions of the limbs, such as talipes, contractures of joints, and congenital high scapula, has for long been recognised. The subject is of interest to general surgeon and orthopædist alike, and any well-attested observation bearing on the question deserves consideration.

It has been realised by many observers that certain congenital deformities of the limbs may be due to shortening of individual muscles or groups of muscles. Attention was frequently directed to this possibility by the older writers on congenital club-foot; and the presence of a shortened muscular or fibrous band uniting the scapula to the skull or to the vertebral column has been a constant finding in all dissections of congenital high scapula. More recently attention has been drawn to the theory that defective growth of the affected muscles might be due to failure in the ordinary sequence of development of striated muscle, incomplete development in a given muscle entailing defective growth and function. Potel,¹ who suggests this possibility, fails, however, to produce convincing evidence in favour of the theory, and no definite microscopic proof of arrest of development of striated muscle has up till now been forthcoming.

Several cases of the deformity known as "arthrogryposis multiplex congenita" have come under the writer's observation. This defect consists of the presence of bilateral club-foot and bilateral club-hand without bony malformation. The deformities are associated with decided limitation of mobility at the joints of the affected limbs. The upper, the lower, or all the limbs may be affected, but the deformity is always bilateral and symmetrical. When the lower extremities are affected, there is, in the majority of cases, a bilateral congenital dislocation at the hip-joints, which is peculiarly resistant to treatment.

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Anatomical observation shows that the joints themselves are normal, and that the limitation of mobility, which is the outstanding feature, is due apparently to want of elasticity of the muscles acting over the joints, the muscles appearing wasted, inelastic, and often more or less contracted.

It is significant that an analogous condition occurs as a lethal hereditary deformity in lambs, and has been closely studied from the point of view of its Mendelian hereditary characters by Fraser Roberts.² Pathological investigations showed that the muscles of the affected limbs appeared atrophied and contracted to the naked eye, but when the muscles were removed by dissection, the joints and their capsules appeared normal and possessed a full range of movement. By the courtesy of Mr Millar of the Institute of Animal Genetics, portions of the affected muscles have from time to time been made available for histological examination, and it was easily shown that they were composed very largely of undifferentiated connective tissue with a considerable degree of fatty change, profusely studded with round or oval cells, each containing a central nucleus, the cytoplasm of which exhibited the staining characteristics of myoplasm. Reference to the appearance of developing striated muscle makes it clear that these cells represent primitive muscle cells such as are met with normally prior to the third month of intra-uterine life. Such an embryonic cell, which is capable of producing one striated muscle fibre, may be referred to as a "myoblast."

A few specimens of muscle have been removed by biopsy from children suffering from arthrogryposis, and, though the advanced stage met with in lambs has not been completely reproduced in the human muscles, there can be no doubt that the muscles are similarly affected. In some cases the muscle has shown large tracts of connective tissue, and there is good reason to believe that, if the muscles concerned had been subjected to examination at birth, instead of some years after, embryonic myoblastic tissue would have been present in these strands. It is not to be expected that such embryonic tissue, incapable of advancing towards perfect development and not in receipt of normal stimuli, would remain unchanged: the tendency must be towards early degeneration, and this is brought about in muscle by a fatty change in the functionless cells, which progresses rapidly after intra-uterine life. In other sections of the affected muscles, areas have been found in which

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muscle fibres, varying greatly in diameter, were completely lacking in striation, either longitudinal or transverse.

The subject was advanced a stage further when a case of apparent absence of the neck muscles on both sides came under the writer's observation. Permission for a biopsy was obtained, and the lower part of one sternomastoid was excised. The muscle was found to be represented by a thin strand of pinkish tissue which on microscopic examination was seen to be composed almost wholly of embryonic myoblast cells.

The main features of the well-known deformity of congenital angling of the tibia consist of a fixed pes equinus and an anterior angling of the tibia at the junction of its lower and middle thirds. On dissection of a fœtus showing this congenital peculiarity it was found that excision of the calf muscles liberated the calcaneus, so that the equinus deformity at once disappeared, suggesting that congenital failure in the growth of the calf muscles had, by their consequent shortening, initiated the equinus deformity, and, when plantar flexion at the ankle-joint had reached its limit, had caused the cartilaginous shaft of the tibia to bend at its weakest part. Unfortunately, the microscopic findings in this case were inconclusive, as the tissue showed too much post-mortem change to allow of an adequate histological study.

Finally, a case of bilateral congenital high scapula was met with in an infant who died of inanition at the age of seven weeks. Clinical examination had shown, associated with a marked degree of high scapula on both sides, a gap in the occipital bone of the unclosed tectal plate variety. A band of muscle could be felt running from each scapula up to the occipital bone on either side of the bony gap. Dissection showed that this muscular band consisted of a portion of the trapezius muscle, the remainder of the trapezius being absent, and possibly an abnormal levator anguli scapulæ and rhomboid muscles. The upper end of the band was attached to the superior nuchal line of the occipital bone, and the conclusion seemed irresistible that the muscular bands had not only held up the scapulæ, but had also prevented the tectal plates of the occipital bone from closing to form the foramen magnum in the normal manner. Histological studies of the band showed the muscle bundles to be separated by wide swathes of connective tissue, and, scattered in fair profusion amongst this tissue, masses of primitive myoblast cells. At the same

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time degenerative changes were seen to be affecting some of the formed muscle fibres at the edge of the fibrous swathes.

It is suggested that such deformities as those investigated result from the failure of certain striated muscles or parts of muscles to undergo their complete course of development, with the result that they remain less elastic, do not grow in length in proportion to the other structures in the limb, and never assume their proper contractility. These abiotrophic muscles must therefore be looked upon as constituting the primary ætiological factor in the production of these deformities.

REFERENCES.—¹ Potel, G., *Traité Pratique d'Orthopédie*, Paris, 1925, Doin. ² Roberts, F. A. Fraser, "The Inheritance of a Lethal Muscle Contracture in the Sheep," *Journ. of Genetics*, April 1929, vol. xxi.

CLINICAL RECORD

CASE OF MYOSITIS OSSIFICANS PROGRESSIVA.

By J. BOYD JAMIESON, M.D., F.R.C.S. ED.

THE paper on this subject by Dr William F. Mair, published in the *Journal* in January and February, leads me to record the following case :

CASE.—L. A. Woman, aged 28. *Family History*.—Father aged 52, healthy. Mother died of pulmonary tuberculosis at the age of 38. A sister, who is healthy, has recently given birth to an apparently healthy child. A brother died at eighteen, of acute uræmia, and was found on post-mortem examination to have the kidneys of a child of eight.

I was present at the birth of the patient and have no note as to any particular difficulty or any possible injury then. It was noticed, however, that her thumbs and great toes seemed to be disproportionately small, and this became more marked as her hands and feet developed. There was also hallux valgus in both feet and the thumbs remained rudimentary.

She remained healthy until the age of four, when she was brought to me with a hard swelling on her back, on the left side, at the level of the second thoracic vertebra. This was painless, extremely hard, and appeared to be firmly adherent to the aponeurosis of the trapezius muscle. Sir Harold Stiles and the late Dr John Thomson saw her, and the appearance of the thumbs and great toes led them to diagnose an early myositis ossificans.

Since then, during twenty-four years, the disease has gradually progressed, and the girl has become more and more helpless as the muscles moving the shoulders, and more recently the hips, knees, and ankles, have become affected. At no time did any soft swelling appear anywhere.

Present Condition.—She is quite helpless, but if placed on her feet is able to "chassez" at a surprising rate across the floor. If leant against a wall she remains *in situ* like a wooden figure. She can be raised by traction on any of the fixed joints without pain being produced. The hands and feet are unaffected, but all the other joints are affected. The lower jaw can be moved one inch, and this fact, with the fortunate loss of two lateral molars, enables her to be fed. Digestion is good. She has a peculiar flattened appearance owing to the gluteal and spinal muscles having been pressed by her weight, and they have apparently

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set in this state. The deeper cervical muscles are soft, the left sterno-cleido-mastoid being much softer than the right. Mentally she is of an extremely happy and bright disposition and has never been known to bewail her lot.

Treatment.—No treatment by the salicylic group or by iodide of potassium had any effect on the condition, but three years ago, when invasion of the masseters threatened starvation, I made a trial of the thiosinamine group and injected min. xv. of iodolysin daily, but had to give this up as her digestion was affected. It is interesting to note that the patient volunteered the statement recently that she was no worse during the last three years, and certainly there appears to be more movement in the lower jaw.

PERISCOPE

THE HEART IN LOBAR PNEUMONIA.

The conclusions formed by the authors of this paper are drawn from an exhaustive study of 975 patients who suffered from lobar pneumonia in various New York hospitals. Although primarily an electrocardiographic study, the results obtained are interpreted in the light of other clinical findings, particularly from the viewpoint of prognosis in this disease. Of the 975 cases, 562 received no treatment with digitalis. Electrocardiograms were obtained at frequent intervals throughout the course of the febrile period and during the early days of convalescence. A total of 7450 electrocardiograms have been analysed.

Clinicians have for years attached much importance to the heart rate in lobar pneumonia, a rapid rate being usually associated with a severe infection and indicative of a poor prognosis. The authors found that nearly two-thirds of those patients with heart rates under 110 per minute, regardless of the day of disease on which the rate was observed, recovered.

Conversely more than two-thirds of those who died showed rates over 110 per minute. This conclusion was further amplified by their construction from the available data of a life expectancy table, which is here reproduced in a modified form from the table given in their paper:—

Heart Rate	Number of Electrocardiograms	Per Cent. Recoveries
70-89	177	90.4
90-109	551	78.1
110-129	495	56.6
130-149	155	31.6
150 and over	25	16.0

The poor prognosis of a high heart rate becomes progressively worse the later it is observed in the disease.

Contrary to what might be expected, it was noted that there was surprisingly little fluctuation in the heart rate during the febrile period, and this in spite of abrupt alterations in temperature. Over 25 per cent. of the cases showed a maximum variation of less than ten beats per minute throughout the disease. Even in the presence of high temperatures, relatively slow heart rates occurred in a fair proportion of cases.

As regards abnormalities of rhythm, auricular fibrillation and auricular flutter were found to be present in 35 instances—(3.6 per cent.) Paroxysmal tachycardia and wandering pacemaker were noted in 51 instances, and as all these arrhythmias were of a paroxysmal nature their frequency is probably under-estimated. Independent of the age at which it is observed—though naturally common after forty years—it is shown that an abnormal rhythm of the heart seriously

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affects the prognosis by its own influence and this frequency bore no relationship to the type of infecting pneumococcus. Extra-systoles, on the other hand, did not appear to have an adverse influence, as the mortality figures associated with their presence were virtually identical with those of the whole group of cases—namely 31.3 per cent. Sinus bradycardia was commonly observed during convalescence.

Partial heart block was observed in 51 cases (9.2 per cent.), dropped beats in three cases, and complete block in none. The interesting observation was made that in 78 per cent. of the cases showing prolonged conduction time, this first appeared after the temperature had reached a normal level. This was not a digitalis effect. Such a state of affairs may be taken as evidence that the disease processes in lobar pneumonia are active in the heart after the temperature has become normal and may remain active for some weeks into convalescence.

A. C. DE GRAFF, J. G. TRAVELL, J. A. YAGER, "An Electrocardiographic Study of the Heart in Lobar Pneumonia" (*Journal of Clinical Investigation*, 1931, x, 633). A. R. G.

ECZEMA AMONG WOODCUTTERS.

Dermatitis among joiners and carpenters is well known, but its occurrence among foresters and woodcutters does not seem to have been recorded in Britain. Spillman, according to Dubreuilh, first described it abroad in 1921, and more recently it has been brought to notice again by Longin. Dubreuilh has seen it several times during the last ten years and publishes six cases in this paper. It attacks the face, hands, and genitals almost exclusively. The hands may be relatively little affected, but they carry the irritant to the face and penis which react rather violently.

The eruption is provoked by the wood with the bark on, and it is the latter which contains the irritant. Neither the planks nor the sawdust have any part in its production. Longin's patients had handled oak and beech. Most of Dubreuilh's patients blamed the oak. One had handled chestnut trees while another was sensitive to the plane as well as to the oak. No case due to pine was seen, though that is the most common tree in the neighbourhood.

Contact with freshly cut wood is not necessary, one of the patients being affected after handling wood which had been lying in the open for a year after being cut. With one exception the patients agreed that it was only when the wood was wet that it was harmful.

The susceptibility to this dermatitis may be acquired and once established is persistent and tends to become more marked.

W. DUBREUILH, "L'Eczéma des Bucherons" (*Annales de Dermatologie et Syphiligraphie*, February 1931, p. 199). R. A.



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OBITUARY

GEORGE MATTHEW ROBERTSON, M.D., LL.D., F.R.C.P.E.,
Hon. F.R.C.S.E.

Physician-Superintendent of the Royal Edinburgh Hospital for Mental and Nervous Disorders; Professor of Psychiatry in the University of Edinburgh.

THROUGH the death of Professor George M. Robertson, which occurred at his home on 28th March, the Edinburgh Medical School has lost one of its most striking personalities. As Physician-Superintendent of the Royal Edinburgh Hospital for Mental and Nervous Disorders and Professor of Psychiatry in the University of Edinburgh, he had established a reputation which was not merely local. For many years he had been a leading psychiatric figure in Scotland and his name was well known in psychiatric circles not only across the Border but beyond the seas. His death will be felt as a personal loss by all, both at home and abroad, who are interested in the care and cure of the mentally disordered. Professor Robertson's health had been failing for some considerable time; and it was no surprise to his friends to learn, a few days before his death, that he had intimated his intention to resign his appointments at the end of the academic year. It is a painful circumstance that this intimation should have been followed so quickly by the news of his death. The large and representative congregation which attended the funeral service at St Cuthbert's Parish Church on Thursday, 31st March, bore witness to the respect in which he was held not only by his medical colleagues but by a wider public.

Professor Robertson was born at Simla in 1864, his father being Colonel John Robertson, C.I.E., a distinguished officer in the Indian Army. His school-days were spent at Madras College, St Andrews, where he attained considerable distinction not only in the class-room but also on the golf-links. After leaving school he embarked at once upon the study of medicine at Edinburgh University, where in 1885 he graduated as M.B., C.M. at the age of twenty-one. It was not, however, until 1913, that he proceeded to the degree of M.D.—which was awarded him with a gold medal for his thesis entitled "Observations on the Early Diagnosis, Ætiology, Prophylaxis, Treatment and Signs of General Paralysis of the Insane." Meanwhile he had obtained the Membership of the Royal College of Physicians (Edinburgh) in 1893 and the Fellowship of the College in 1895.

No sooner had Professor Robertson obtained his medical qualification than he was appointed a Resident Physician in the Royal Edinburgh Infirmary. It was during his tenure of this appoint-

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ment that his interest first became directed to that branch of medicine to which he subsequently devoted his whole life. Having decided where his bent lay, he set out with characteristic thoroughness to acquire the best possible equipment for the practise of his future speciality. Accordingly, when the term of his appointment at the Royal Infirmary expired, he entered upon a course of post-graduate study which was sufficiently broad to include not only psychiatry but also the allied sciences of neurology and pathology. During this period his time was spent partly in Edinburgh and partly in London—in Edinburgh at the Pathology Department of the University, and in London at the Bethlem Hospital and the National Hospital, Queen's Square.

Professor Robertson's active career as a psychiatrist began in the institution with which he was later to be so closely identified in the capacity of Physician-Superintendent; for, after the period devoted to post-graduate study, he became Assistant Physician in the Mental Hospital at Morningside—"The Royal Edinburgh Asylum for the Insane," as it was then officially designated. Here Robertson had the good fortune to serve his apprenticeship with no less distinguished a psychiatrist than Sir Thomas Clouston, under whose superintendship the institution was already becoming famous. Sir Thomas was quick to appreciate his young assistant's varied abilities and he assigned to him many responsible tasks, not only in the administration of the hospital and the instruction of students but in the prosecution of scientific enquiry. The confidence which Sir Thomas placed in him may be judged by the fact that he entrusted him with the task of supervising a new edition of his own famous text-book. Sir Thomas also delegated him to visit Bernheim's Clinic at Nancy and Charcot's Clinic at the Salpêtrière to investigate the possible applications of hypnotism to the treatment of the insane. Robertson's report on this subject was presented by Sir Thomas Clouston to the British Medical Association Committee on Hypnotism, of which Sir Thomas was a member, in 1890. In the same year Robertson was awarded the Gaskell Prize of the Royal Medico-Psychological Association—an award to be followed in 1892 by that of the Association's Bronze Medal.

At the age of twenty-eight he already found himself in full charge of a mental hospital; for in 1892 he was appointed Medical Superintendent of the Perth District Asylum at Murthly. It required but a short experience of the responsibilities of a superintendent to inspire in Robertson that profound interest in the welfare of the mentally afflicted, which was so characteristic a feature of his professional life. It was at Murthly that he learned to view with dissatisfaction many of the conditions prevailing in the asylums of

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the day and that he began to formulate the ideal which he later came to describe as the "hospitalisation of the asylum" (a phrase which he appears to have been the first to employ). Henceforward, under the inspiration of this ideal, he took his place in the front rank of the reformers. One of the important innovations which distinguished his régime at Murthly was the introduction of the villa system of housing—a system which proved so successful that, when the Edinburgh authorities came to consider the plans for a new mental hospital at Bangour, Robertson was appointed the Medical Assessor. A still more important innovation, however, was the introduction of hospital-trained nurses into the wards of the institution. This measure was difficult to effect owing to the reluctance of such nurses to undertake asylum duty. Eventually, however, several were secured; and the first hospital nurse to work in the wards of an asylum among insane patients was appointed by Robertson at Murthly in 1896.

In 1899 he relinquished his charge at Murthly on being appointed Medical Superintendent of the Stirling District Asylum at Larbert. Here he found another opportunity to exercise his zeal for improving the conditions under which mental illness was treated. Within a year of his appointment he had arranged for a group of male patients to be placed under the sole charge of female nurses, by night as well as by day. This was the first time that male patients had ever been placed unreservedly under the care of female nurses for twenty-four hours a day at any mental hospital. The success of this experiment led to its adoption as a standard practice in the male wards. What with the whole-time care of male patients by female nurses and the employment of hospital nurses in the asylum wards, Robertson was able to claim that by 1901 the ideal of "hospitalisation" had been organised into a working system at the Stirling District Asylum.

In 1908 he was appointed to succeed his old chief, Sir Thomas Clouston, as Physician-Superintendent of the Royal Edinburgh Asylum at Morningside—an appointment involving the charge of two separate institutions (Craig House and The West House respectively). It is no easy task at the best of times to administer two separate institutions with efficiency, but the fact that Robertson was called upon to fill the shoes of so distinguished a predecessor made the task doubly formidable. Events proved, however, that the task was by no means beyond his capacity. The fact that the great prestige enjoyed by these institutions under Sir Thomas Clouston should have been not only maintained but increased under Dr Robertson's superintendentship is eloquent testimony to the efficiency and progressiveness of his administration. At Morningside he found another field for the achievement of complete hospitalisation and, through his initiative, "The Royal Edinburgh Asylum for the Insane" became "The Royal

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Edinburgh Hospital for Mental and Nervous Disorders," both in name and in fact.

The complete hospitalisation of Craig House and The West House was, however, only a further application of methods which Robertson had already begun to employ in his previous charges. In order that we may appreciate the full extent of his subsequent contributions to the mental welfare of the community, we must look outside rather than inside these institutions; for it was characteristic of him that his vision was not limited by the walls of the mental hospital. So far was this from being the case, indeed, that one of his most notable achievements was the establishment of facilities for the treatment of mental disease outside the mental hospital and the initiation of measures calculated to prevent the development of psychotic conditions. In Edinburgh he was fortunate in having a Board of Managers who were not only free from the restrictions which hamper a public authority, but who took a particularly liberal view of the functions assigned to them in the Charter of their Corporation. Their enlightened attitude made it possible to give effect to a number of original schemes conceived in Professor Robertson's fertile brain. Of these schemes one of the most important was that which resulted in the provision of a series of nursing homes in Edinburgh and district for the treatment of the milder forms of mental illness without certification. These nursing homes are run, so far as possible, on the same lines as ordinary medical nursing homes, and patients entering them may be attended, if desired, by their own doctors or by any physician whom they may select. The establishment of such homes was a complete innovation, and the scheme was only carried out in the face of formidable difficulties. The opportunity to give effect to his scheme for providing nursing homes arose out of the circumstances of the Great War. At the time, public sentiment was averse to the idea that men who had suffered mental break-downs in the defence of their country should be subjected to the stigma of certification and detention in asylums; and, as it was known that the Morningside Board was endeavouring to establish nursing homes, the Board was approached to provide accommodation for a number of such cases outside the boundaries of the mental hospital. Accordingly a home for officers suffering from mental symptoms was opened in Craiglea Place in 1917. Professor Robertson pointed out, however, in his Annual Report for 1917 that there was no essential difference between the case of a soldier who becomes insane in the defence of his country and that, for example, of a woman who develops puerperal mania in childbirth. In accordance with this principle, the officers' home was thrown open at the end of the War, for the reception of civilian patients—a step to which, fortunately, no legal objection could



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GEORGE MATTHEW ROBERTSON

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be taken owing to the presence of the provision entitled "Schedule G" in the Scottish Lunacy Act of 1857. A second home was opened in Comiston Drive in 1919 and others have been opened at varying intervals. At the time of his death eight such homes were under his supervision.

Another important scheme originated by Robertson was that which led to the opening of the Jordanburn Nerve Hospital on 11th April 1929. The success of the nursing homes had convinced him that there existed a widespread public demand for the treatment of the milder psychoses and the graver neuroses outside the walls of a mental hospital. The nursing homes, however, were of necessity only available to those who could afford to pay nursing home fees; and the Jordanburn Hospital was instituted with the object of providing patients of restricted means with similar facilities to those enjoyed in the nursing homes. One of the chief features of the Jordanburn scheme was the provision of an Out-patient as well as an In-patient Department. In this way it became possible to extend the benefits of the hospital to patients suffering from neurotic and psychotic symptoms at the incipient stage before any form of institutional treatment became necessary. The Jordanburn Hospital thus embodied the ideals of preventive, no less than of remedial, medicine in their application to the sphere of mental and nervous disease. The usefulness of the institution was increased by the fact that from the beginning it was run in conjunction with the Mental Out-patient Clinic at the Royal Edinburgh Infirmary—a clinic which was opened in 1923 upon the appointment of Professor Robertson as first occupant of the post of Physician-Consultant in Psychiatry to that hospital. The Jordanburn scheme was also intended from the outset to further the interests of preventive medicine by providing a centre of research upon the nature, origin and treatment of mental and nervous disease—an intention made evident in the official designation of the institution as "The Jordanburn Nerve Hospital and Psychological Institute." It was the first institution of its kind to be established in Great Britain and, so far as can be ascertained, in the world.

Perhaps the best illustration of Robertson's devotion to the ideals of preventive medicine as applied to mental and nervous disease is to be found in his responsibility for the opening of the "Edinburgh University Psychological Clinic for Children and Juveniles" at 37 Morningside Park, in a building adjacent to Jordanburn. The primary object of this clinic is to attack those deviations of thought and behaviour, which lead in later life to insanity and neurosis as well as to crime, at the source of their origin in childhood. The clinic was intended for the investigation and treatment of "the problem child" in every sense of the term—whether the problem be one of nervous symptoms, undesirable habits, school retardation, school discipline,

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home discipline or delinquency. A psychological clinic of an informal character had already been in operation for eight years at the Psychology Department of Edinburgh University under the auspices of Professor Drever; but, owing to the limited resources at Professor Drever's disposal, the work of the clinic was only carried on under serious limitations. Professor Robertson was so impressed, however, by the value of the work actually performed by this clinic that he proposed to his Managers that they should make themselves responsible for the housing and maintenance of the clinic under more favourable conditions. The Board readily acceded to this proposal, and, with the whole-hearted co-operation of Professor Drever, the new clinic was opened on 18th February, 1931. As events turned out, this was the last important scheme to be carried into effect by Professor Robertson before his death; but it is difficult to believe that it really would have proved to be the last, if he had been granted an additional lease of life and health.

Professor Robertson was not only a pioneer in all matters connected with the treatment and prevention of mental disease, but a prominent teacher of psychiatry. Throughout the Larbert period he collaborated with Sir John Batty Tuke in the conduct of regular classes on psychiatry at the School of Medicine of the Royal Colleges in Edinburgh. While the theoretical lectures were delivered in Edinburgh, the Stirling District Asylum at Larbert was utilised for clinical instruction; and the fact that students up to the number of a hundred were prepared to travel to Larbert and back for a clinical lecture is eloquent testimony both to the popularity and proficiency of Robertson's teaching. Upon his appointment to the superintendship of the Royal Edinburgh Asylum in 1908 he became associated with Sir Thomas Clouston as a lecturer at Edinburgh University; and in 1910 he was appointed full Lecturer in Mental Diseases by the University authorities. In 1920, when the lectureship was accorded professorial status with the help of an endowment from the Managers of the Mental Hospital, he became the first occupant of the new Chair—and incidentally the first Professor of Psychiatry to be appointed in this country. During his occupancy of the Chair he was responsible for arrangements whereby his own course of lectures on mental disease was supplemented by courses on psycho-pathology and psychology.

As a writer Professor Robertson never produced any considerable work; for his gifts were personal and practical rather than literary and academic. He was, however, a frequent contributor of articles to the medical journals. These articles were always worth reading; and particular mention may be made of those entitled "Hypnotism at Paris and Nancy" (*Journal of Mental Science*, October 1892), "Hospital Ideals in the Care of the Insane" (*J.M.S.*, April 1902), "The Employment of Female Nurses in the Male Wards of Mental

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Hospitals in Scotland" (*Edinburgh Medical Journal*, March 1916), and "The History of the Teaching of Psychiatry in Edinburgh" (*E.M.J.*, April 1923). The majority of his articles were devoted to the discussion of practical measures for the treatment and prevention of mental disease, to the suggestion of reforms in asylum practice and in the law relating to insanity and to the education of medical opinion in matters of mental health. Many of his articles were of considerable historical interest: for no one possessed a greater knowledge of the history of psychiatry than Professor Robertson. So great was his knowledge of this subject that upon occasion he was able to correct French writers in matters relating to the history of psychiatry in France.

With reference to Robertson's writings, it is to be noted that he attached almost as much importance to his Annual Reports on the institutions under his charge as he did to his articles in the medical journals. His Annual Reports were addressed to the general public; and he regarded them as providing him with an opportunity both to educate public opinion on matters of mental health and to interest the ordinary citizen in the reform of the laws relating to insanity. It was characteristic of him that he regarded the education of public opinion as supremely important for the promotion of mental welfare; and on this account he was an enthusiastic supporter of the National Council for Mental Hygiene and the Scottish Association for Mental Welfare from their inception. He was a member of the Councils of both these bodies, and he was selected as one of the representatives for Great Britain at the First International Congress on Mental Hygiene at Washington in 1930.

In view of Professor Robertson's distinguished career as a psychiatrist it was only natural that he should have been the recipient of various honours. As instances of the recognition he received at the hands of his fellow psychiatrists may be mentioned the facts that he was President of the Royal Medical-Psychological Association for 1922 and Maudsley Lecturer for 1926 (the subject of his lecture being "The Prevention of Insanity"). He was also a Corresponding Member of the Société Médico-psychologique de Paris and Vice-President of the "Centenaire de Bayle," which was held in Paris in 1925 on the hundredth anniversary of Bayle's original description of general paralysis of the insane as a clinical entity. His distinction was also recognised in various ways by the Royal College of Physicians in Edinburgh. He was elected President of the College for 1925-27, and in 1930 he was awarded "The Cullen Prize for the greatest benefit done to Practical Medicine." He was also three times selected as Morrison Lecturer. The various subjects of his lectures were "Melancholia: the Depressive Phase of Manic-Depressive Insanity"

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(1911), "Recent Observations relating to General Paralysis of the Insane" (1913), and "Sir Alexander Morison and the Teaching of Psychiatry in Edinburgh" (1927). While President of the College of Physicians he was elected Honorary Fellow of the College of Surgeons in Edinburgh, and in 1931 the University of St Andrews conferred upon him the honorary degree of LL.D.

As a man Professor Robertson was characterised by a genial personality which made him deservedly popular. Always an acute observer of human nature, he showed at times an astonishing insight into the motives of others; yet he was slow to revise his estimate of any one about whom he had once formed a favourable opinion. He had a gift of diplomacy which enabled him to carry through difficult negotiations with remarkable success; and this gift, together with his boundless enthusiasm, contributed in no small measure to the fruition of his schemes. His enthusiasm, his versatility and a certain *penchant* for the spectacular were sometimes felt more appropriate to a Gallic than to a Scottish environment; but, after all, he was French on the maternal side; and it is perhaps to his French blood that he owed some of those qualities which made him so successful an advocate of every measure calculated to lighten the burden of insanity. His inspiration at any rate was derived largely from the French tradition; for his great hero was Pinel; and it was at his initiative that a bust of Pinel was unveiled at the West House by the French Ambassador on 26th September 1930. Pinel's insistence that a lunatic was above all a patient found its logical outcome in the ideal of "the hospitalisation of the asylum" which was so dear to Robertson's heart. As in the case of Pinel, the key-note of Robertson's achievement lay in a whole-hearted and disinterested devotion to the welfare of all who suffered from mental disease. It was to the furtherance of this end that all his other gifts were harnessed.

Essentially an innovator and a reformer at heart, Professor Robertson had not so much an original as an adaptable mind. His scheme for nursing-homes and his Jordanburn scheme show how quick he was to sense the presence of a popular demand and how skilful he was in devising measures to supply it. The guiding idea of his life was the relief and prevention of mental disease and he saw everything in relation to this idea. In his endeavour to give it practical expression he was distinguished by a capacity to mobilise to his aid ideas originating from the most diverse sources. It was this open-mindedness and adaptability, combined with an intimate knowledge of human nature, an unbounded enthusiasm and an uncompromising devotion to the cause of mental welfare, that made him so notable a figure in the realm of Scottish psychiatry.

W. R. D. F.

NEW BOOKS

The Commoner Nervous Diseases. By FREDERICK J. NATTRASS, M.D. (Dunelm), F.R.C.P. (Lond.). Pp. 218, with 19 illustrations. London: Humphrey Milford, University Press. 1931. Price 12s. 6d.

Text-books of neurology contain details of so many complicated anatomical and physiological facts, and consider so many symptoms, signs, and diseases which are of great rarity, that the practitioner has difficulty in obtaining the information he requires with regard to the common nervous diseases. In this book the features of the commoner nervous diseases are described so clearly and in such simple language that all can appreciate the points on which diagnosis is based. Prognosis and treatment are also carefully considered. The book is written by an experienced neurologist who has based his method of approach to the subject on his experience of post-graduate teaching.

The description of the methods of examination, which is usually so unnecessarily complicated, is here made simple, and yet remains quite adequate for all ordinary requirements. The value of the book would have been increased by including a description of the physiological principles on which neurological examination is based, but this is a minor criticism of a book which will be welcomed by both students and practitioners.

Herz und Angst. By Professor Dr LUDWIG BRAUN. Pp. 119, with 1 illustration. Vienna: Franz Deuticke. 1932. Price 9s.

Although the German "Angst" has no exact equivalent in English, it corresponds roughly to "anxiety." The author takes as the classic expression of "Angst" the anxiety experienced during an attack of angina pectoris. He finds some degree of "anxiety" to be characteristic of all patients suffering from cardiac disease and tries to show that "anxiety" bears a specific relationship to disorder of cardiac function (the heart being as much the organ of "anxiety" as the eye is the organ of vision). A qualitative distinction is drawn between "anxiety" and fear:—fear being an emotional reaction to outer dangers (real or imagined), while "anxiety" is the experience of an internal menace to life originating in what has been always recognised as *the* vital organ. "Anxiety" is thus an experience in which the idea of impending dissolution is always implicit and which is commonly associated with explicit ideas of death.

The author's thesis is well expounded and is supported not only by clinical observations but also by references to etymological research and quotations from general literature illustrating the natural

Notes on Books

connection which exists in the human mind between "anxiety," "heart" and "death." The problems of neurotic anxiety are inadequately dealt with, but the author provides an interesting and stimulating treatise.

Nutrition and Physical Fitness. By L. JEAN BOGERT, Ph.D. (Instructor in Experimental Medicine, Yale University). Pp. 554, with 64 illustrations. London: W. B. Saunders Company, Ltd. 1931. Price 14s.

Though primarily written for those with no previous knowledge of food chemistry or physiology, Dr Bogert's book should prove of value to all who are interested in everyday nutritional problems. The text is written in non-technical language but the author's teaching has a thoroughly scientific foundation. Physiological processes, nutritional requirements (under various conditions), food values, meal planning, and many other subjects are explained. The uses of vitamins and mineral salts are convincingly taught and food faddists are severely dealt with. Diet in sickness occupies a small part of the book, but suitable dietetic measures for dealing with obesity, malnutrition, constipation, and many other conditions are briefly and helpfully discussed.

NOTES ON BOOKS

Flatfoot, by S. D. Fairweather, M.A., Ch.B. (Bale Sons, & Danielsson, 7s. 6d.) The central theme of this monograph is that flatfoot and other concomitant foot troubles are not due to high heels or low heels but to *heels*. The evil effects of modern foot-wear are discussed, the theory of the mechanism of walking is dealt with, and a heelless boot is described and its advantages set forth. The case for the heelless shoe, properly made, is strong, but, as Sir Robert Jones states in the preface—"The difficulty will be in defeating the habits of centuries of fashion."

The Clinical Interpretation of Aids to Diagnosis. Vol. II. (The Lancet, Ltd., 10s. 6d.) The material in the present volume is of the same high standard as that of its predecessor. It is slightly more abstruse, such subjects being dealt with as, for instance, the blood cholesterol and blood phosphorus, the microscopic findings in certain skin lesions, and the clinical significance of slit-lamp appearances. The needs of every-day medical practice are kept strictly in mind, and the avowed aim of the series should continue to be fulfilled, namely the securing of the most fruitful possible partnership between the laboratory worker, or highly specialised clinician, on the one hand, and

Books Received

on the other those whose work necessarily compels their interests to be more diffused. We commend this volume as heartily as we did its predecessor.

The Essentials of Bacteriological Technique, by R. F. Hunwicke, B.Sc. (Lond.), A.I.C. (Williams & Norgate, 6s. 6d.), contains some useful practical instructions with regard to certain points of bacteriological technique, for example, the use of filters, methods for eliminating unnecessary work in the production of culture media, and good, short accounts of the routine bacteriological examination of milk, water, meat and canned foods. For the rest, the book is made up of short and superficial descriptions of some of the technical methods of bacteriology, but it does not cover the essentials from the point of view of research or of any form of diagnostic work. A chapter, of two and a half pages, on the "Diagnosis of certain Diseases" is inadequate, misleading and in places inaccurate with regard to the bacteriological diagnosis of six infectious conditions.

A Text-book of Medicine for Nurses, by E. Noble Chamberlain, M.D., M.Sc., M.R.C.P. (Humphrey Milford, 20s.). Opinions may well differ as to whether it is possible or even desirable for the nurse to assimilate during her training so much theoretical matter as is contained in this volume. If, however, it is to be regarded as a book of reference to which the senior nurse may turn for information regarding any special disease with which she may come into contact, then it may be heartily commended. The author writes clearly and has managed very successfully the difficult work of condensation. The volume is finely printed and the illustrations are well reproduced.

BOOKS RECEIVED

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|---|---------------|
| BIGGER, JOSEPH W., M.D., Sc.D. (Dublin), F.R.C.P.I., D.P.H.,
M.R.I.A. Handbook of Bacteriology. Third Edition.
(Baillière, Tindall & Cox, London) | 12s. 6d. net. |
| CHEESMAN, J. E. Baillière's Synthetic Anatomy. Parts I. to XII.
(Baillière, Tindall & Cox, London) | 42s. net. |
| COLLIE, Sir JOHN, C.M.G., M.D., J.P., Lt.-Col. R.A.M.C. Fraud in
Medico-Legal Practice . . . (Edward Arnold & Co., London) | 10s. 6d. net. |
| CONYBEARE, J. J., M.C., M.D. (Oxon), F.R.C.P. Text-Book of Medicine
by Various Authors. (Second Edition).
(E. & S. Livingstone, Edinburgh) | 21s. net. |
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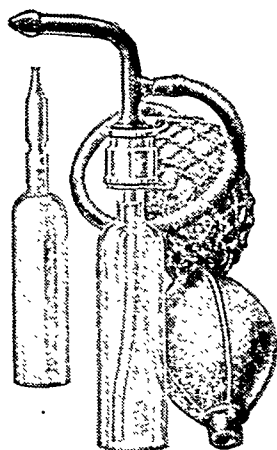
- GALLICHAN, WALTER M. *The Critical Age of Woman.*
(Noel Douglas, London) 4s. 6d. net.
- GIFFORD, SANFORD R., M.A., M.D., F.A.C.S. *A Handbook of Ocular Therapeutics.* (Henry Kimpton, London) 15s. net.
- GRANGER, AMÉDÉE, K.C.B., K.C.I., M.D., F.A.C.R. *Para-Nasal Sinuses and Mastoids.* (Henry Kimpton, London) 25s. net.
- HARMAN, MARY, T., Ph.D. *A Text-Book of Embryology.*
(Henry Kimpton, London) 18s. net.
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- League of Nations. *Quarterly Bulletin of the Health Organisation.*
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(George Allen & Unwin, Ltd., London) 2s.
- MACMURCHY, HELEN, M.D. (Tor). *Maternal Care* (The Little Blue Books Leaflet Series). Department of Pensions and National Health, Ottawa, Canada.
- MARSHALL, C. F., M.Sc., M.D., F.R.C.S. *A New Theory of Cancer and its Treatment* (John Wright & Sons Ltd., Bristol) 3s. 6d. net.
- The Medical Annual, 1932* (John Wright & Sons Ltd., Bristol) 20s. net.
- MEYER, WILLIAM H., M.D. *Clinical Roentgen Pathology of Thoracic Lesions* (Henry Kimpton, London) 28s. net.
- Royal Victoria Hospital Tuberculosis Trust *Annual Report (1930-31).*
- SAMSON, EDWARD. *Oh Doctor!* (John Murray, London) 2s. 6d. net.
- SANGER, MARGARET, and HANNAH M. STONE, M.D. *The Practice of Contraception* (Baillière, Tindall & Cox, London) 21s. net.
- SHRUBSALL, F. C., M.A., M.D., F.R.C.P., D.P.H., and A. C. WILLIAMS, M.R.C.S., L.R.C.P., D.P.H. *Mental Deficiency Practice* (University of London Press, Ltd., London) 12s. 6d. net.
- SOLLMANN, TORALD, M.D. *A Manual of Pharmacology.* Fourth Edition (W. B. Saunders Company, London) 37s. 6d. net.
- Survey of a Quarter of a Century of the Treatment of Alcoholism and other Drug Habits, being the Twenty-Fifth Report of the "Rendlesham" and "Beckenham" Branches of the Norwood Sanatorium Limited.
- SUTTON, DON C., M.S., M.D., and HAROLD LUETH, Ph.D., M.D. *Diseases of the Coronary Arteries (Myocarditis).*
(Henry Kimpton, London) 25s. net.
- Transactions of the American Gynecological Society for the year 1931.*
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- TRUMPER, MAX, Ph.D., and ABRAHAM CANTAROW, M.D. *Biochemistry in Internal Medicine.*
(W. B. Saunders Company, London) 27s. 6d. net.
- Tuberculosis in South African Natives, with Special Reference to the Disease amongst the Mine Labourers on the Witwatersrand.* The South African Institute for Medical Research, Johannesburg.

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PEPTIC ULCER AND ITS TREATMENT: A STUDY OF 200 HOSPITAL CASES.*

By ALEXANDER GOODALL, M.D., F.R.C.P., Physician-in-Ordinary
to the Royal Infirmary of Edinburgh.

THE peptic ulcer of stomach and duodenum is an important

The Transactions of the Medico-Chirurgical Society of Edinburgh

SESSION CXI.—1931-1932

has been made on the following grounds:—(1) X-ray evidence when available. (2) The incidence of pain.

In gastric ulcer, the pain is usually high in the epigastrium, near or to the left of the middle line. The pain in duodenal ulcer is lower down and may lie to the right of the middle line. In gastric ulcer, the onset of pain is usually within half an hour of taking food and may be immediate. Patients are often afraid to eat. In duodenal ulcer, onset of pain is late. It seldom occurs earlier than two hours after a meal and may not occur till the stomach is nearly empty. Thus, patients often complain of pain in the early hours of the morning, and "hunger

* Read at a Meeting of the Medico-Chirurgical Society on 3rd February 1932.

† I wish to acknowledge the work of my House Physicians in connection with the investigation and recording of these cases, and the valued help of Sisters Grant and Pennycook in their treatment.

Alexander Goodall

pain" is now regarded as a characteristic symptom. When the distinction between gastric and duodenal ulcer is made on these grounds, it is noted that other points of distinction emerge.

Of the 200 cases, 43 were regarded as gastric and 157 as duodenal ulcer.

	Male.	Female.	Total.
Gastric	26	17	43
Duodenal	141	16	157
			<hr/> 200 <hr/>

	Average Age.	Average maximum free acidity.
Gastric	39 (72-22)	34.9
Duodenal	36.7 (71-19)	54

In contrast with the sex incidence of twenty-five years ago, gastric ulcer has come to be more common in males. Duodenal ulcers retain their great male preponderance.

The most striking difference has been found in the gastric acidity. Fractional test meals were examined in practically all cases. It seemed unnecessarily laborious to compare these curves in their entirety; and it appeared that the general course of the curve had a relation to the maximum free acidity, whether that occurred in the fasting juice or at the end of half an hour or one hour. The average figures show a definitely greater acidity in the duodenal cases, and in cases diagnosed as peptic ulcer we would be disposed to regard low acidity as an indication that the site was the stomach. The distinction between gastric and duodenal ulcer is not carried further, and our subsequent review refers to peptic ulcer, wherever placed.

Sex and Age Incidence.—Of the 200 cases, 167 were males, 33 females. Their ages ranged from 71 to 19; the average was 37.

Occupation.—The outstanding fact is that 27, or 13.5 per cent., of the ulcer patients were miners. This figure must, however, be regarded with caution, since the hospital serves a large mining community, and other statistics differ.

In Luff's analysis of 1389 cases, the occupation list is headed by mechanics and skilled artisans, 22 per cent. Miners are ninth on his list with 4 per cent. Of the 2000 admissions (male and female) to my charge, 6.6 per cent. were miners. Of the 2000, 1.3 per cent. were miners suffering from duodenal ulcer. Of the total admissions to hospital (surgical and medical, male and female), 14.2 per cent. were miners and (shale) oil workers.

Peptic Ulcer and its Treatment

The influence of "carried meals" may be a factor, but when motor men and tramwaymen are added, the total muster is only 7, and when we add the engineers, smelters and moulders as representing "heavy" workers the figure is again 7. The remaining general company includes a chef.

Duration.—Patients usually give a history of very prolonged disability. Stomach trouble for twenty years is not unusual. The duration is tabulated below:—

	Cases.
Not exceeding 1 week	1
Over 1 week, not exceeding 1 month	2
„ 1 month, „ „ 6 weeks	5
„ 6 weeks, „ „ 3 months	8
„ 3 months, „ „ 6 months	8
„ 6 months, „ „ 1 year	9
Total under 1 year	33
Total over 1 year	167
	<hr/> 200

Average duration of history, 5.2 years (one week to twenty years).

Previous Operation.—Seven patients gave a history of previous gastro-enterostomy, and two others had been operated on for perforation of an ulcer. Eight patients had been operated on for appendicitis.

State of the Teeth.—In 92 cases the teeth are classified as bad, in 44 as good, and 64 patients had complete dentures. Doubtless many of the latter were a belated improvement.

Wassermann Test.—This was carried out in 130 cases, with 8 positive and 122 negative results. It cannot be said that the positive results were associated with any obvious departure from the common clinical picture or course.

Symptoms.—Classified in terms of the patient's chief complaint we tabulate the cases:—

Pain	86
Hunger pain	61
Pain and vomiting	42
Vomiting	3
Hæmatemesis	3
Melæna	1
Anæmia	3
Debility	1
	<hr/> 200

Alexander Goodall

Hæmatemesis was recorded in 49 cases and melæna (overt or occult) in 73.

It may be noted that cases of perforation are not sent to the physician. On the other hand, cases of suspected but non-existing perforation are not infrequently sent to the surgeon. One would not wish it otherwise.

A striking point is the rarity of vomiting as a single symptom and the comparative infrequency of vomiting accompanied by other symptoms. I have come to regard vomiting as a somewhat urgent symptom, and if it is not allayed within four days a consultation with a surgeon is desirable. A very small ulcer may maintain severe vomiting, but I have not seen this since modern methods of treatment have been carried out. The usual explanation is pyloric stenosis, but this diagnosis should be reached without much difficulty. The microscopic and chemical examination of the gastric contents, the charcoal test, and X-ray examination should make the condition clear.

X-ray Examination.—This was carried out in 179 cases. The chief finding is stated as an ulcer when a definite niche or crater was seen. The results were:—

Ulcer	36
Deformed duodenal cap	80
Residue after 6 hours	45
Negative	18
	<hr/> 179

It will be noted that evidence of ulcer in the form of a niche or crater is reported in only 20 per cent. of the cases. In all of these the diagnosis was not otherwise in doubt. The X-ray, however, is valuable in confirmation; and when an ulcer crater is seen to disappear on successive examinations, we have very convincing and gratifying evidence of progress. It must not be assumed that an ulcer crater filled with granulation tissue is necessarily covered with epithelium.

Cases occur, however, which not only cast doubt on the value of the X-ray shadow but on the soundness of all our inferences. I quote, in brief, Case 1560.

A miner, aged 30, was admitted on 12th February 1929. For twelve months he had suffered from pain in the mid-line and left of the epigastrium, coming on two hours after food. Pain was temporarily relieved by more food or baking soda.

RADIOGRAMS SHOWING STAGES IN THE HEALING OF ULCERS (Case 031).

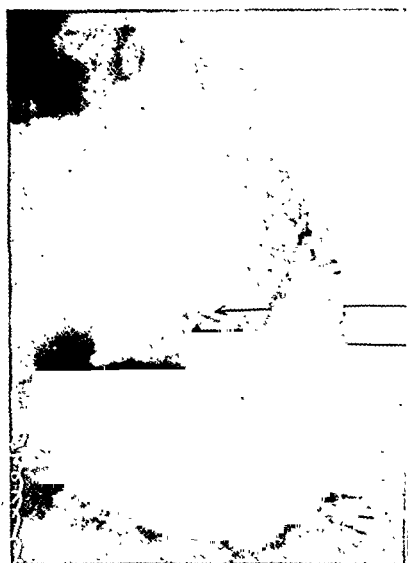


FIG. 1.—Large ulcer on lesser curvature with an air bubble in the fundus of the ulcer.

FIG. 2.—The same stomach 1 week later.



FIG. 3.—The same stomach 5 weeks later.

FIG. 4.—The same stomach 8 weeks later.

RADIOGRAMS SHOWING STAGES IN THE HEALING OF ULCERS (Case 685).

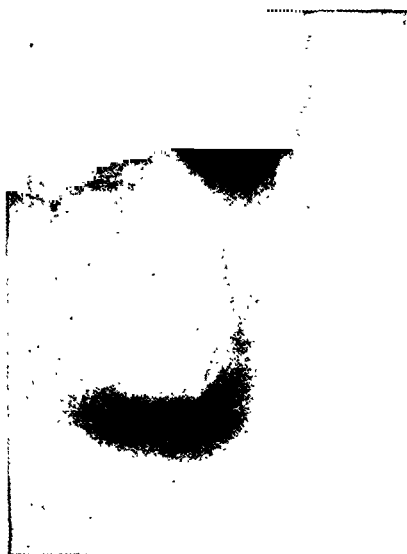


FIG. 1.—Large penetrating ulcer on the lesser curvature.



FIG. 2.—The same stomach 2 weeks later.



FIG. 3.—The same stomach 5 weeks later.

Peptic Ulcer and its Treatment

He was sometimes awakened by pain between midnight and 1 A.M. He had never vomited but had noticed the stools black in colour. Teeth were bad. Fasting juice showed a high free and total acidity. Benzidine test of faeces positive. The radiologist's report read:—"Stomach of normal position and active peristalsis but poor tone. There was a sharply-defined incisura on lateral aspect of pyloric antrum, and in the recumbent position an hour-glass formation of the fundus. The duodenal cap was definitely irregular. Six hours' atonic gastric residue with residual flake in cap. Examination indicates a duodenal ulcer."

Patient was discharged free from symptoms on 15th March 1929. A return of symptoms kept him off work in July and August 1929, in January and February 1930, and in May 1930. He came back to the ward in December 1930. He complained of pain and vomiting, and his description suggested haematemesis. Again he did well and gained 6½ lb. in weight, but in view of repeated disability in spite of his alleged adherence to directions, and the X-ray finding, we sought surgical advice. Mr Struthers operated on 6th January 1931 and kindly reported as follows:—"The abdomen was opened. Stomach and duodenum were thoroughly examined and the only lesion discoverable was a very small induration about half-way along the lesser curvature. One or two enlarged glands were found near this, and it seemed to represent either an active or a healed ulcer. Stomach was opened and the indurated area exposed and examined and found to represent a scar without any breach of surface at all. Stomach was accordingly closed and nothing further was done. Duodenum was healthy: gall-bladder was healthy. Patient has three or four old-standing calcareous glands in the right iliac fossa."

Bolton¹ states he has seen two cases operated on for a persistent niche, and depressed scars only were found. "Deformed cap" is the usual report. When it is associated with tenderness it is probably a finding of some significance. In a few instances I have had a report alleging a duodenal pouch. In the only case I submitted to a surgeon the pouch proved to be a figment of the radiological imagination.

A gastric residue after six hours is a very important finding. It has the initial advantage that the shadow really corresponds to the substance. If the residue is large, some degree of pyloric narrowing may be inferred; but the small residue by no means

Alexander Goodall

necessarily implies stenosis and often disappears after a course of treatment. Rapidity of emptying as indicative of gastric irritability, and delay in emptying as indicative of atony or pyloric spasm, would alone make X-ray examination worth while. The practitioner who has a patient X-rayed "to see if there is an ulcer" is likely to be disappointed.

Treatment.—There is a consensus of opinion that peptic ulcers, as their name implies, are due to auto-digestion. Why this auto-digestion of stomach and duodenum should occur is a mystery. Why it should not always occur is even a greater mystery. Immediately after death the gastric juice usually begins to digest the gastric wall. It is not enough, however, to say that living tissues can resist digestion. A pike on occasion disgorges a partly digested but still living frog. Be this as it may, the most successful treatment is based on the fact that peptic digestion can only occur in an acid medium. For many years the physician has prescribed alkalis, but it is only in recent times that treatment by diet and alkalis has been placed on a satisfactory basis. The alkaline treatment usually took the form of the administration of bicarbonate of soda in a bitter infusion after meals. The very efficacy of the soda as an ant-acid greatly diminishes its value. Its solubility leads to its immediate or early neutralisation, and in a comparatively short time the gastric contents are again acid. This doubtless gave rise to the curious teaching, not yet dead, that sodium bicarbonate actually leads to an increased output of hydrochloric acid in the gastric juice. There is no evidence² to support this notion, except perhaps a misinterpretation of "climbing" acidity curves in fractional test meals, and there is no known factor in pharmacology which might explain it.

Various systems of diet have been introduced with a view to keeping the contents of the stomach alkaline or neutral by means of frequent feeds. The Lenhartz³ system is the best known of these. Sippy⁴ makes use of a system of frequent feeding and an intensive administration of alkalis. While Sippy's system is complicated, its introduction did a great deal to call attention to the possibility of a better outlook for the ulcerated dyspeptic than had previously been offered.

The system of progressive additions to the diet has been criticised by Hurst,⁵ and others, on the ground that if a diet is suitable for an ulcerated surface it should remain suitable till that surface is healed. This proposition may be accepted

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as far as it goes, but it seems to fall before the slogan "safety first."

We never know how near to perforation a patient may be. It seems, therefore, that the initial diet must be bland, smooth, and small in amount, even at the expense of a shortage of caloric value and a constant loss in weight. On the assumption that the danger of perforation is over at the end of a week of suitable treatment, we then modify the diet to afford a larger supply of energy, and at the same time to be bland enough to suit a raw but no longer acutely dangerous area. A considerable addition to the healing process may be postulated by the end of the second week, and a further improvement of the diet may be made.

How this is done, and how, thereafter, a damaged organ is to be restored to health and fitness to act again as the portal of entry of the fuel for a healthy and vigorous machine, is a problem which may meet with very diverse solutions. Dietetic directions are necessarily empirical, and are mainly influenced by personal experience. It is a great advantage to keep general directions simple. They then possess the double advantage of being widely applicable and of being easily amended to meet special cases. We have followed on general lines the recommendations of MacLean, Jones, and Fildes.⁶ The directions are as follows:—

Directions.

First Week.—Eight oz. of citrated milk are taken every two hours from 6 A.M. to 10 P.M. The milk is citrated by dissolving one 10 gr. tablet of sodium citrate in a little hot water and adding it to the milk. Benger's Food may be added to some of the feeds if desired. After each feed one level teaspoonful of alkaline powder stirred into water should be taken. An extra teaspoonful should be taken after the 10 P.M. feed, and at any other time, day or night, if pain or discomfort is felt.

Second Week.—Meals are taken every three hours from 6 A.M. to 9 P.M.

6 A.M. Citrated milk, 8 oz.

9 A.M. Citrated milk, 8 oz. ; strained porridge, 4 oz.

12 noon. Citrated milk, 4 oz. ; baked or steamed custard (one egg) ;
cream, 2 oz.

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- 3 P.M. Cup of weak tea with cream ; slice of crisp toast, buttered when cold.
- 6 P.M. Citrated milk, 8 oz. ; one switched egg (which may be added to the milk), or one lightly boiled or scrambled egg with small portion of toast, buttered when cold.
- 9 P.M. Citrated milk, 8 oz.

After each meal the alkaline powder should be taken as in the first week.

Third Week.—Meals are taken every three or four hours from 6 A.M. to 9 P.M.

- 6 A.M. Citrated milk, 8 oz. ; one switched egg (which may be added to the milk), or one lightly boiled egg ; slice of toast, buttered when cold.
- 9 A.M. Strained porridge, 4 oz. ; cup of weak tea with cream ; one slice dry toast, buttered when cold.
- 1 P.M. Steamed fish (plaice, sole, haddock, or whiting), 4 oz. ; boiled rice, 1 oz. ; milk pudding (rice, cornflour, arrowroot, etc.), one large saucerful ; cream, 2 oz.
- 4 P.M. Cup of weak tea with cream ; slice of crisp toast, buttered when cold ; one egg, poached, scrambled, or lightly boiled (may be postponed till 7 P.M. if preferred).
- 7 P.M. Citrated milk, 8 oz. ; slice brown bread and butter ; a few rusks.
- 9 P.M. Citrated milk, 8 oz.

The powder is taken after meals as before.

Fourth Week.—Chicken or rabbit may replace the fish at 1 P.M., and fish may be added to the meal at 7 P.M. Cauliflower (not stalks), young sprouts or other green vegetable, passed through a sieve, may be taken at 1 P.M. A small helping of potato may be taken if it is not followed by discomfort.

The powder is taken at 9 A.M., 1 P.M., 7 P.M., and bedtime.

Fifth Week and Afterwards.—Patient may return to ordinary meal times. A little underdone beef or mutton may be added. The powder may be omitted except at bedtime. If any discomfort is felt, the patient should revert to the directions of the third week.

The following substances should be avoided:—

Uncooked vegetables and fruit ; soup, beef tea and meat extracts ; pickles, pepper, savouries, sauces, and spices.

Patients are strongly advised to avoid both alcohol and tobacco. Smoking before meals is particularly harmful.

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Formula for Alkaline Powder.

Sodium Bicarb.	1 oz.
Magnesium Carb. (pond.)	2 „
Calcium Carb.	2 „
Bismuth Oxycarb.	$\frac{1}{2}$ „

Dispensed in wide-mouthed bottle. The formula can be had in liquid or tablet form if required.

Further Points in Treatment.

These directions may be given to a doctor, nurse or patient, but of course may require modification.

Pain may be very persistent. This is often due to spasm, and the administration of 5 to 10 minims of tincture of belladonna three or four times daily is often a great help. Granted a correct diagnosis, it is very seldom that these measures fail. There is, however, a type of patient who has a "conditioned reflex." He has so long suffered from pain at a certain interval after meals that he still experiences the pain although the local condition that originated it has cleared up. A particularly difficult patient is the one who has been assured by his doctor that "he will never be right till he has had an operation." As a rule, even in the worst cases, the resistance of the reflex paths may be sufficiently increased by the action of some bromide to lead to a speedy cure. The number of cases who received belladonna was ten. Three of these had bromide in addition, and one patient had bromide only.

Operations have not infrequently been performed for persistent pain, and in some cases the pain has been relieved. I am convinced, however, that pain persisting after a few days of alkaline and antispasmodic treatment is never due to an uncomplicated ulcer. I have known cases operated on for pain alone and nothing abnormal has been found. Some of these cases may be relieved, but operation is a very uncertain remedy for pain which may be due to persistence of a reflex or a conditioned reflex, or to a mental error. Such cases add many recruits to those who "sit on the door step" of a consulting room. It is to be regretted that they seldom remain faithful to the door step of the surgeon who added injury to a sensorium previously insulted.

In hospital, it is an immense help to catering and nursing to admit ulcer patients in batches. Ten per cent. of our cases suffer from gastric or duodenal ulcer. Their stay in

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hospital is usually three weeks, which is four days less than the average stay of all patients. On the other hand, cases with hæmatemesis and other urgent symptoms have to be admitted as emergencies, and these increase the average stay of all ulcer cases to thirty-four days. We therefore arrange to admit ulcer cases from the waiting list up to 10 per cent. of our bed capacity every three weeks. The actual number varies with the clamancy of the list in other directions and with the emergency admissions for ulcer.

It is very seldom that hospital patients complain or ask for extras. Private patients do not have the advantage of seeing their brothers in affliction: they are a little more prone to "ask for more." One seldom makes concessions during the first four days. Thereafter one weakens, and the second and third "weeks" may consist of four days each. If patients ask for fruit, one allows a very small experiment in the fourth week. Patients vary very greatly. If a small portion of banana causes no discomfort, the experiment may be extended. A small portion of a ripe pear, a strawberry, or a little orange juice, may be tried and the quantity increased in the event of success. A dash of good sherry is a grateful addition to the switched egg and milk. A little ale may be tried after the fourth week if keenly wished. Champagne and whisky invite trouble and the invitation is usually accepted.

Action of Alkalis.

The composition of the alkaline medicine has been very fully discussed in recent times. The sodium bicarbonate is freely soluble and strongly ant-acid. It is therefore very potent, but its efficacy is of short duration. It is claimed that the CO_2 liberated from the bicarbonate in an acid stomach has a useful sedative action. In magnesium carbonate we have an even more powerful ant-acid. Its solubility is less, and therefore it comes into action after the soda, and persists in action after the soda has been broken up. In similar manner this is followed by the still less soluble carbonate of lime. The oxycarbonate of bismuth is a comparatively poor ant-acid reagent and has the disadvantage of being costly.* Its former

* The prices of the ingredients of the powder are as follows:—

Sodium Bicarb.	4d. per lb.
Magnesium Carb. (pond.)	1s. 4d. „
Calcium Carb.	7d. „
Bismuth Oxycarb.	13s. „

Peptic Ulcer and its Treatment

reputation for depositing a protective layer on an ulcer is now doubted, although radiologists show us flakes of bismuth on "ulcer craters." I would omit it if necessary on the ground of expense: otherwise I prefer to retain it. It has been a valued drug for many generations. It has a sedative action—none the less for being unexplained—and it reinforces the chalk in counteracting any tendency to diarrhœa set up by the magnesia. Following Sippy, some authors prescribe the powders in separate combinations—soda and magnesia in one and bismuth and chalk in the other—and these are taken on alternate days or in some other arrangement. I have never found this necessary and can only recall one or two cases in which the proportions of the powder were altered on account of diarrhœa.

It may be noted that the formula suggested and many modifications are to be obtained in the form of cream or emulsion and also in the form of tablets. The latter are very useful in the case of patients who have returned to work and do not have some of their meals at home.

It may also be noted that faulty teeth and pyorrhœa must be dealt with if one has hope of curing any form of dyspepsia.

Complications.

Stenosis.—It has been already stated that vomiting, if persistent, is to be regarded as a symptom requiring explanation. I have not seen it occur after the alkaline régime had been in operation for two days except in cases of pyloric stenosis. Persistent vomiting alone may be a sufficient indication for surgical intervention, since the vomiting may prevent the obtaining of other evidence. It may be pointed out that the existence of a large gastric residue after six hours is not necessarily evidence of stenosis, but it is by no means a rule that definite evidence of stenosis is an indication that medical treatment will fail. At the present time I have in hand a patient, aged 71, who suffered from severe pain and occasional vomiting. The stomach occasionally stood out in spasm after palpation and fully two-thirds of a barium meal was still present after five hours. A dilated aorta and high blood-pressure were among several considerations that went to contraindicate surgery. After two days of rest in bed on milk and alkalis, all symptoms disappeared; and at the end of three weeks the patient was eating fish and chicken and had no discomfort.

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Even in cases where there is visible peristalsis, symptoms may entirely clear up. It would appear that œdema and spasm often play a large part in the induction of stenosis. There are cases, of course, where it is desirable, even imperative, to relieve stenosis by operation as soon as possible. Although symptoms are often allayed, even when narrowing is considerable, it may remain doubtful whether a patient can return to his usual occupation. For this reason we advised operation in six of the 200 cases.

Hæmatemesis and Melæna.—Apart from what may be regarded as the emergency treatment of these conditions, their existence does not materially alter the usual routine. Starvation does not stop the secretion of gastric juice, and the accumulation of fasting juice probably does more harm than the administration of citrated milk. A few hours after hæmatemesis, small feeds of milk, followed by alkali, are begun.

Perforation.—When the intensive alkali treatment was first introduced, it was often said that the method was dangerous as it masked symptoms and perforation would become more common. As a matter of fact it has become less common. Sippy⁴ states that he has never seen perforation after the second day of treatment. I have never seen it at all.

Alkalosis.—This is largely a myth. I have only seen it occur when there is pyloric stenosis with vomiting. Stieglitz⁷ maintains that it may also occur in nephritis. Severe headache, nausea, vomiting, and dryness of the mouth are the symptoms. Even if they occur, no great harm is done. The alkali should be withheld for a day or two, and thereafter the powder might be given without the sodium bicarbonate. The calcium would then unite with chlorine in the gastric juice, and the resulting calcium chloride tends to act as an acid in the body.

Course.

To those of us who were accustomed to see many cases of peptic ulcer treated on "light diet" with sodium bicarbonate and a bitter, thrice daily, the results under the persistent alkali régime seem extraordinary. It is very seldom that any symptoms persist after the second day. On the fourth day, the patient's mental outlook is completely altered. Instead of the miserable and rather sour expression of the chronic dyspeptic, there appears what I call the "alkaline smile." This is apt to be followed by a little anxiety about the menu, but

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the assurance of promotion to "second week" diet is a sufficient sedative.

During the first week the average patient loses about 4 lb. in weight. At the end of the third week he is usually about 4 lb. to the good. Patients are generally allowed up after the second week, but the actual time is determined in each case.

The great majority of our patients go from hospital to a convalescent home and usually stay three weeks.

Again, the contrast between the present and past régime is striking. On reporting, the past-day patient would grudgingly admit that he was "not bad." Asked if he felt fit for work, he would seldom admit working capacity. The present-day patient returns feeling and looking fit. He not merely admits capacity but boasts of it. In these days his cheeriness about his health is often pathetically altered by the reflection that "there's no job to go to."

Since the modern treatment has been introduced, the number of patients who take the trouble to come back to the wards to express their gratitude has been a most pleasing feature. In former times I cannot recall one, apart from those who had obtained benefit from a gastro-enterostomy done to relieve stenosis.

Failures.

The immediate results of the alkaline treatment are so uniformly good that the first inference that occurs to us in the event of failure is a wrong diagnosis. The cases admitted during the period under discussion as "duodenal ulcer" and subsequently found to have some other condition numbered ten.

The list is as follows:—

1. Appendicitis with pyloric spasm.
2. Duodenal ileus.
3. Duodenal adhesions of unknown origin.
- 4 and 5. Malignant disease (2 cases).
6. Gastric atony with pain and with vomiting at long intervals.
7. Cirrhosis of liver with pain after food and persistent melæna.

(All of these were discovered or verified by operation.)

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8. Persistent hæmatemesis, with X-ray evidence of pyloric stenosis. (No lesion found at operation.)
9. Early tabes dorsalis.
10. Megrim.

Other failures were three in number and were due to complications:—

1. Pyloric stenosis and appendicitis for which operation was refused.
2. A severe gynæcological affection.
3. Mental derangement.

We might add as an "extra" a "hospital bird" who, in spite of the lesson of a previous perforation, was found throwing away his medicine.

After-results.

MacLean⁸ states that since 1924 he has not had a single instance of an ulcer recurring at the site at which it was formerly present as indicated by radiograms, that out of seventy cases admitted in a year none required operation, and that during the course of a year only one case formerly treated had been readmitted. This seems an amazingly favourable picture of hospital results.

Among my 200 cases I have had six readmissions. These are as follows:—

1. CASE 235/826.—Car driver (unemployed), aged 28, had suffered from epigastric pain for eight years. X-rays showed a completely atonic stomach of obstructive type and a deformed duodenal cap. Had operation for appendicitis. Admitted 21st August 1928. Symptoms cleared up, but in view of large residue was referred to Mr Graham who performed gastro-enterostomy. Symptoms returned in two months. Cleared up on further treatment. Returned with previous symptoms on 7th August 1929. Weight precisely the same as on first admission. No further information regarding him, but doubtless continued unemployment and unsatisfactory home conditions tend to reproduce the causes of his initial illness.

2. CASE 13.—Did well. Had recurrence of symptoms following an alcoholic bout two years later. Again cleared up rapidly.

3. CASE 694/1639.—Paper maker, aged 35, admitted on 7th June 1929. Good recovery. Readmitted February 1931. Slight relapse.

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4. CASE 1322.—Miner, aged 47, had severe pain with free acidity of 90. X-rays showed an ulcer crater and a large residue. Symptoms cleared up, but patient returned as bad as ever in four months. He was referred to Mr Stuart, who found a duodenal ulcer and a swollen appendix.

5. CASE 649.—Painter, aged 31, admitted on 4th May 1929 with hunger pain, high acidity, deformed cap and residue. Readmitted with a return of symptoms on 12th October 1931.

6. CASE 116.—Labourer, aged 42. Ten years' history of hunger pain, and recent hæmatemesis, admitted 31st May 1928. Four weeks in ward. Left without symptoms. Stopped taking alkaline powder in August. Perforated at midnight on 8th December 1928. Operation Dr Paterson, Kirkcaldy. Returned with pains as before on 6th August 1929.

These results might be regarded with some complacency but unfortunately they do not reflect the true picture. Dr E. L. Farquharson, in the course of an investigation, has written to 118 of the 200 cases and has received replies from ninety-eight. Of these ninety-eight cases, all of whom had been discharged without symptoms, thirteen have since undergone operation. The remaining eighty-five patients answered the following questions in the proportions stated below.

- | | |
|---|--------------|
| (a) Completely cured. Can eat anything. No pain. | |
| Able for full work | 15 per cent. |
| (b) Greatly improved. Occasional slight pain or discomfort. Able for full work | 47 „ |
| (c) Improved, but have frequent attacks of indigestion, and have always to be careful with diet. Able for light work | 31 „ |
| (d) Constantly troubled with indigestion, and can eat very little. Unable for work. (One of the latter seen recently looked stout and well nourished) | 7 „ |

These results compare unfavourably with those obtained in private practice. The great trouble is that hospital patients after a course of treatment return to the conditions that originated their illness. Malnutrition due to unemployment and a mental complex fostered by the dole are among causes militating against permanent good results. In many homes girls are not taught to cook, with the result that their husbands have to endure a life of gustatory martyrdom on bread and boiled tea. In addition to seventy peptic ulcers, I admit to my wards at least one case of scurvy per annum!

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Discussion and Conclusions.

Several important studies of peptic ulcer have appeared within the last four years. MacLean and Hurst dealt with medical aspects in 1928, and Moynihan⁹ followed with a keenly critical lecture on problems in gastric surgery in which medical aspects were also discussed. Bolton followed in 1930, and Rendle Short¹⁰ with a statistical inquiry in 1931. Luff's¹¹ collective investigation of the after-history of gastro-enterostomy appeared in 1929-30. Such differences as exist between these and between other writers are more differences of detail than of essentials. All are agreed that every uncomplicated case of peptic ulcer should receive medical treatment in the first instance. There is some agreement that after a second relapse surgical intervention is indicated, and there is a large and increasing body of opinion that gastro-enterostomy alone is not adequate treatment of ulcer.

The forebodings of those who predicted danger in the modern application of medical treatment have not been borne out.

The principles underlying the modern treatment are not new, and in some measure the practice also had been followed, but it may safely be said that it is only within the last four years that an adequate combination of dietetic and medicinal treatment has become general.

By suitable dietetic and medicinal treatment, the symptoms of peptic ulcer can be allayed and the dangers of perforation and severe hæmorrhage overcome well within fourteen days. If pain persists after fourteen days, the condition is not uncomplicated ulcer.

Unless the complication be detected and operation offers a definite prospect of relief, no operation should be undertaken. Moynihan writes with wisdom: "By drugs and diet no harm is done to an ulcer which exists only in the mind of the healer. Grievous and irreparable harm may be done by the act of the surgeon, and his art brought thereby into disrepute."

After three weeks of home or hospital treatment and three weeks of convalescent treatment, the overwhelming majority of ulcer patients express themselves as fit for their usual occupation. This gives rise to our greatest difficulty. Again, to quote Moynihan, "The treatment of gastric and duodenal ulcers in the mass is now an economic rather than a medical problem."

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We know how rapidly granulation tissue fills up the floor of any ulcer. We also know how long it may take the epithelium to spread in from the edges. Has our candidate for work got a firmly healed ulcer? Even if he has, and his septic teeth have been removed, and by some miracle he has dentures which he wears in his mouth and not in his pocket at meal times, can he put up a better fight against work in a wet mine, life in a damp house, the problem of maintaining his family, poor food, and bad cooking than he could when his duodenum first gave way? Is he any better off if his ulcer be excised and his scar be fortified by the best quality of suturing material? I know not, but I know this—that from the fourth day of the treatment outlined, the day of onset of the “alkaline smile,” that man has been living down an “inferiority complex” as far as his digestion is concerned, and I affirm that in the modern treatment of peptic ulcers there has arrived unostentatiously but surely one of the big advances of medicine.

REFERENCES.—¹ Bolton, *Brit. Med. Journ.*, 1930, i., 727. ² Cushny, *Pharmacology and Therapeutics*, 541. ³ Lenhartz, *Med. Klin.*, 1907, iii., 405. ⁴ Sippy, *Journ. Amer. Med. Assoc.*, 1915, lxiv., 1625. ⁵ Hurst, *Brit. Med. Journ.*, 1928, ii., 779. ⁶ MacLean, Jones, and Fildes, *Lancet*, 1928, i., 14. ⁷ Stieglitz, *Arch. Intern. Med.*, 1928, xli., 11. ⁸ MacLean, *Brit. Med. Journ.*, 1928, i., 619. ⁹ Moynihan, *Brit. Med. Journ.*, 1928, ii., 1021. ¹⁰ Rendle Short, *Brit. Med. Journ.*, 1931, i., 435. ¹¹ Luff, *Brit. Med. Journ.*, 1929, ii., 1074, 1125, 1212; 1930, i., 348.

DISCUSSION.

Professor Murray Lyon said that he shared Dr Goodall's enthusiasm for the modern methods of treatment in cases of peptic ulcer. If the case is a simple one, relief from symptoms is obtained practically at once and usually before the fourth day. This rapid improvement occurs so constantly that if pain persists after the first day or two the diagnosis should be revised. Some patients appear to be rather susceptible to the usual doses of magnesia and may begin to complain of a new pain, situated lower in the abdomen than the original one and of a rather different character. By having the alkalis in two different mixtures, the patient can soon learn to use them in such a way as to keep both the stomach and the bowels right. In spite of the enormous quantities of alkali sometimes consumed, the danger of alkalosis appears to be very slight. With regard to dieting, the criticism may be offered that the use of citrated milk affords the patient rather a poor caloric intake. Much better results are to be obtained by feeding with equal quantities of milk and cream, which

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greatly increases the value of the diet and allows the patient to gain strength more quickly.

Professor W. T. Ritchie indicated that 300 cases of ulcer of stomach and duodenum had been under his care in the Royal Infirmary during a period of ten years. For two or three days after a hæmorrhage, a patient receives nothing except rectal injections of glucose saline, four-hourly, and morphine subcutaneously. Thereafter he is given successively albumin water, whey, citrated milk, and mixtures of milk and cream, before cereals are permitted. Alkalis are never given except when the patient fails to improve under the influence of rest and diet alone. The administration of alkalis is a confession of failure; the claims that have been advanced in support of alkaline therapy are extravagant and unjustified. Chronic cases that are refractory to dietetic treatment, and all relapsing cases, should not be buoyed up with false hopes regarding the curative power of alkalis but should have the undoubted benefit of surgical treatment.

Dr Fergus Hewat said—During the past six years I have had under my care, in Chalmers Hospital, a large number of patients suffering from gastric symptoms. In many cases I have had great difficulty in making up my mind whether the patients had or had not unequivocal gastric or duodenal ulcers. Fractional test meals were carried out in all these cases, and in about 15 per cent. no free acid was discovered. These achlorhydric cases were given, in the first instance, a stimulating line of treatment—dilute acid, nux vomica, etc.—in accordance with text-book routine, and, with practically no exception, their symptoms were aggravated by this treatment. Theoretically sound treatment having failed, intensive alkaline treatment was then adopted, with, to my astonishment, extremely satisfactory results. It would therefore appear that intensive alkaline treatment is beneficial in achlorhydric cases—presumably non-ulcer cases—as well as in those cases where a certain diagnosis of ulcer can be made. It seems to me highly probable that the mere rest in bed and simple diet are the two points which really matter in the treatment of patients who have symptoms pointing to gastric ulcer. In the past I have not had, at Chalmers Hospital, the opportunity that I am looking forward to having, when that Hospital re-opens, of the detailed X-ray investigation which, in the absence of frank hæmatemesis or persistent melæna, is nowadays considered essential in many clinics before a clear-cut diagnosis of gastric ulcer is made.

Like other physicians, I have great difficulty in persuading ulcer patients to continue treatment—dietetic and medicinal—for a sufficiently long period: they leave hospital so free of symptoms that there is not much inducement to adhere for more than a few weeks to the

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restrictions advised on leaving hospital. I try, during the last week in hospital, to give as far as possible a line of treatment which can be carried out at home; and I therefore agree with Dr Goodall's outlook in trying to feed the patient without cream, which is such an expensive item in the dietary of the working man or the unemployed.

Dr Goodall has been fortunate in not having had to deal with a case of alkalosis. I have had two doctors under my care who suffered from this condition. One of them was a picture of abject misery while the state of alkalosis lasted, and this state of affairs handicapped his progress and delayed his recovery.

Dr Somerville said—I would like to ask Dr Goodall whether the cases, after they left hospital, still carry on with alkaline treatment. I find that though able for full work, they have to continue their alkalis. One patient takes $1\frac{1}{2}$ lb. alkaline powder every month and has never lost a day's work for over three years. I do not know of one peptic ulcer patient who has been able to give up alkaline treatment.

Dr W. A. R. Thomson said—I have recently been going over a series of cases of peptic ulcer, none of which have received massive alkaline treatment, and I thought it might be of some interest to the Society to give a brief summary of this series. The series consisted of 275 cases, of which 187 were duodenal ulcers and 88 were gastric ulcers.

Gastric ulcers.—Of the gastric ulcers 57 received medical treatment, 24 were treated surgically, and 7 died of extensive hæmatemesis shortly after admission. Of the cases treated surgically, two died shortly after operation, giving a mortality rate of 8 per cent., while the remainder made satisfactory recoveries, and, so far as we know, have never suffered from any recurrence of symptoms. Of those medically treated, 42, or 75 per cent., received dietetic treatment alone, 13 were given alkalis occasionally, while two received alkalis and belladonna. Of all the cases, 34 per cent. were admitted on account of hæmatemesis within six days, and of these 20 per cent. died. Eight per cent. of all the cases were admitted to the ward on more than one occasion; approximately half of those were ultimately operated upon, while the other half responded to medical treatment.

Duodenal ulcers.—Of the cases with duodenal ulcers, 54 received surgical treatment, while 133 received medical treatment. Of the cases treated surgically 3 died, giving a mortality rate of 6 per cent., while the remainder made satisfactory recoveries and with one exception suffered from no recurrence of symptoms. Of those medically treated, 94, or 70 per cent., received dietetic treatment alone; 28 were given alkalis occasionally; 6, alkalis and belladonna; and 5, belladonna alone.

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Of all the cases 15 per cent. were admitted with a history of gross hæmatemesis within six days, and of these, 25 per cent. died—the actual cause of death in one-third of these being perforation. Thirteen per cent. of all the cases were admitted to the ward on more than one occasion, and of these approximately half were ultimately operated upon, while the remainder responded to medical treatment.

Though this summary is merely approximate, it would seem to suggest that satisfactory results can be obtained in the treatment of peptic ulcer without the intensive use of alkalis, and that if a case does not respond to careful dietetic treatment, with possibly the addition of occasional alkalis, further treatment should be in the hands of the surgeon.

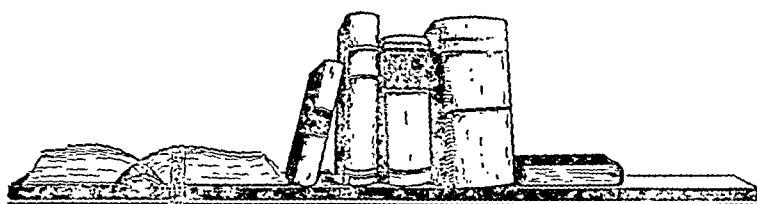
Mr J. M. Graham also spoke.

Dr Goodall, in reply, said that he agreed with Professor Murray Lyon about the value of cream as an addition to the milk diet. He was, however, catering for hospital patients and he preferred to train them on a dietary they were likely to obtain at home. He did not think it greatly mattered whether the ulcer diet was a ladder of a few or of many rungs or was merely a scaffolding. The important thing was to order something definite. Until something more convincing than auto-digestion was discovered as the explanation of peptic ulcer, he thought alkaline treatment should be given. He thought that the white powder which Mr Jardine saw pouring out through duodenal perforations had been taken in the vain hope of relieving pain *after* the perforation.

Meeting—20th January 1932.

MR GEORGE CHIENE, F.R.C.S., President, in the Chair.

The following were admitted Members of the Society: William Davidson, M.B., Ch.B.; E. Leslie Farquharson, M.B., F.R.C.S.E.; R. H. Watson, M.A., M.D., B.Sc.



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MENSTRUATION IN MENTAL DISEASE.*

By GILBERT I. STRACHAN, M.D., F.R.C.P., F.R.C.S., F.C.O.G.,
and IAN SKOTTOWE, M.D., D.P.M.

IN investigating menstrual conditions in the insane it has to

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investigation which the authors have carried out on the general relationship between mental and gynaecological disease and, at an early stage of this investigation, it became evident that the menstrual aspect was one of the most important of the whole matter.

Our investigation was carried out on 250 consecutive female admissions to Cardiff City Mental Hospital. These cases were all examined and classified in the first place from the mental point of view and, then, later and independently, from the gynaecological point of view. They were all women of adult life.

Regarding the menstrual conditions certain criteria were laid down. Normal menstruation was taken to indicate menstruation occurring every four weeks and lasting some four or five days. By menorrhagia we mean the persistence of

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the event for more than seven days and in speaking of scanty menstruation we indicate a duration of less than two days. By irregular menstruation is indicated an irregularity not of a few days but of several weeks and this term would be typically illustrated in a case whose periods had occurred on one occasion three weeks after the previous period, followed by another period some eight weeks later. Amenorrhœa is, of course, self-explanatory; while we use the term dysmenorrhœa to describe only those cases with severe pelvic menstrual pain. Cases with only vague discomfort are not included.

It would appear useful at this stage to discuss *the mental conditions met with* and the terms used in describing them. To those who do not specialise in psychiatry one of the terrors of that subject is the varied and complicated nomenclatures employed. On this account a particular mental condition may be described so variously by different writers that confusion is caused to the general medical reader; while, for the same reason, a connected study of the literature becomes difficult.

We have adopted a simple psychiatric classification evolved by one of us (I. S.) in which the cases are classified thus:—

Schizophrenia.—This term indicates a splitting of the mind in which the emotional state bears little or no relation to what the patient thinks, so that she may describe intense agony yet with a cheerful manner and expression of face. *Dementia præcox* is included here and, with some writers, the terms are almost synonymous.

Affective Disorders.—In these there is an excessive display of emotion in any direction. This may be *manic* and many cases of so-called puerperal mania are included here. Or the emotion may be one of *depression* and a large proportion of cases of melancholia come under this category. Or again the mental state may alternate from a manic to a depressed condition producing the well-recognised *manic-depressive insanity*.

Paranoid State.—By this term is indicated a condition of *delusions or hallucinations* of a personal character persisting in a state of clear consciousness and with no sign of a gross affective disturbance. By the term *Organic Psychoses* we mean mental derangement which appears to be secondary to some organic pathological lesion, cerebral or situated elsewhere in the body. The main type of mental aberration exhibited in these cases is *confusion* and this confusional symptom may indicate the organic basis of the mental disease. A very

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extended clinical investigation, however, is often necessary before the organic cause can be determined.

In cases of *Mental Deficiency with or without Psychoses*, there is such a defect of reason from birth or from early age that the individual cannot maintain her place as a social unit.

Certain *Miscellaneous Cases* are included. These comprise several epileptic cases with mental disease and one case of psychoneurosis.

From the psychiatric point of view then, the cases may be tabulated in this way:—

1. Schizophrenia	54 cases.
2. Affective Disorders—	
Depressed	70
Manic	27
Alternating	4
	— 101 „
3. Paranoid State	45 „
4. Organic Psychoses—	
With Organic Brain Disease	2
With other Bodily Disorder	24
	— 26 „
5. Mental Deficiency with or without Psychoses	17 „
6. Miscellaneous Cases—	
Epilepsy with Psychosis	4
Epilepsy with Mental Deficiency	2
Psychoneurosis	1
	— 7 „
	<u>250 cases</u>

It is in relation to this classification that the mental aspects of our cases are considered.

In discussing the menstrual disorders met with, we have included only cases in which no organic lesion was present. Thus, if menorrhagia was found in association with fibrosis or with a fibroid of the uterus, the organic causal factor would be evident and the menstrual disorder would thus appear to have less association with the mental condition present.

Again, it was felt that it would be of value, as a control, to know the proportion of patients presenting themselves in ordinary gynæcological practice with functional menstrual irregularities comparable to those found in our series; for these purposes of comparison a series of one thousand sane gynæcological cases were investigated and the comparative figures for the number under discussion obtained. It would

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have been even more valuable for purposes of comparison and control, had it been possible to ascertain such data in a similar number of the presumably normal female population.

It was found that, of these 250 cases, 61—24·4 per cent.—were at or beyond *the menopause* while 189 were in menstrual life. In investigating our series of non-psychotic gynæcological patients, the percentage beyond the menopause was only 10 but the proportion of patients in the post-menopausal period of life appears to be high in mental hospitals; thus Healey, investigating 474 cases of mental disease in the female, found 231—almost 50 per cent.—beyond the menopausal age.

But we cannot consider post-menopausal mental disease in this communication; we have to discuss

Mental Disease in Menstrual Life.—In our 189 cases in this period of life the mental conditions were:—

Affective Disorders	66 cases
Schizophrenia	49 "
Paranoid State	31 "
Organic Psychoses	20 "
Mental Deficiency	16 "
Miscellaneous Cases	7 "
	<u>189 cases</u>

Two of these—a melancholic and a schizophrenic—were pregnant, so 187 cases fall to be considered.

Associated with these mental states were found the following menstrual conditions:—

Menorrhagia	14 cases	7·5 per cent.
Scanty Menstruation	13 "	6·9 "
Amenorrhœa	11 "	5·8 "
Dysmenorrhœa	6 "	3·2 "
Irregular Menstruation	4 "	2·1 "
Irregular and Profuse Menstruation	3 "	1·6 "
Late Puberty	2 "	1·1 "

Thus menstrual abnormalities were present in only 28·4 per cent. of these cases, menstruation being normal in 134 cases. Further, it will be noted that the most common condition in this respect was not amenorrhœa but the reverse condition of menorrhagia and that amenorrhœa comes only third in the series. These findings do not support the usually accepted view that amenorrhœa is the most common menstrual abnormality in mental disease and they are not in line with observations made by others. Thus Ross in 1909, investigat-

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ing 395 mental patients, found amenorrhœa in 95 cases—just over 24 per cent.—and irregular menstruation in 83 cases—just over 21 per cent.—while J. F. Healey in 1928, examining 243 patients at the menstrual age, found amenorrhœa in 14.2 per cent., dysmenorrhœa in 20 per cent., and menorrhagia in 12 per cent. of his cases.

In the series investigated by Ross menstrual derangements were present in one-third of the cases and she quotes Esquirol and Morel to the effect that derangements of menstruation form one-sixth of the physical causes of mental disease.

This subject may be further considered by discussing it in terms of the menstrual irregularities and the associated mental conditions or, in the reverse, by discussing the mental conditions primarily and the associated menstrual irregularities. Before this society the first course would seem to be the more appropriate.

Functional Menorrhagia was present in 14 cases—7.5 per cent. of 187 cases—while in the control non-mental series the proportion was 1.3 per cent.

The associated mental conditions were

Schizophrenia	5 cases
Affective Disorders—	
Manic	4
Alternating	1
	— 5 "
Mental Deficiency	3 "
Paranoid State	1 "
	— 14 cases.

Menorrhagia was present also in four other cases with signs of cervical infection or chronic metritis, but these are not included here.

Now there were 54 schizophrenics of whom five were post-menopausal, so that the incidence of menorrhagia in this condition is just about 10 per cent.; while in the affective disorders the proportion was 5 out of 66 menstruating cases—7.5 per cent.

It is of interest to note that 10 of these 14 cases were single and nulliparous. Regarding age, six were under 30 years, five were between 30 and 40, and only three were over 40 years of age.

The mental course was usually not good and only three cases recovered—melancholia, schizophrenia and paranoid—

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while one died and one became worse. In three cases the mental condition improved while in six cases there was no change.

Improvement in the menstrual condition, when it did occur, was capricious, often temporary, and bore no relationship to treatment, to the mental condition, or to mental improvement.

Scanty Menstruation was found in 13 cases, 6.9 per cent. and in the control series in 1.3 per cent.

The mental conditions present were—

Affective Disorders—			
Depressed		5	
Manic		2	
		—	7 cases
Paranoid State		3	”
Schizophrenia		2	”
Organic Psychoses		1	”
		—	13 cases.

In two of these there was some irregularity of menstruation. The main conditions in this category were the affective disorders and especially melancholia and in these conditions the incidence of scanty menstruation was seven out of 67 cases in menstrual life—10.5 per cent.

Of these 13 cases, seven were nulliparous and six had borne children while the age varied from 24 to 49, four being over 40 years of age. The indications were that these last four cases were approaching the menopause.

Five of the cases showed no improvement, three were improved, three have been discharged recovered—paranoid state, melancholia and organic psychosis—while two have died.

In five of these cases thyro-ovarian extract was administered, in two cases a small erosion was scraped, while in the other six cases no special gynæcological treatment was given; the menstrual results were indefinite and the mental results did not appear to be influenced.

Amenorrhœa is one of our most important considerations in view of the opinion so commonly expressed in text-books, that it is frequently or even usually found in association with mental disease.

It will be noted that in our series it occurred in 11 cases—5.8 per cent.—while in the controls the percentage was 1.9. This hardly bears out Novak's statement, quoted earlier in this paper, although the figures of Ross and of Healey, previously mentioned, are much higher than ours.

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The following mental conditions were present in these amenorrhœic cases:—

Affective Disorders—

Depressed	3	
Manic	1	
Alternating	1	
—	5	cases
Schizophrenia	4	„
Paranoid State	1	„
Organic Psychosis	1	„
—	11	cases.

The ages of these cases varied from 19 to 45 years, and the period of amenorrhœa from three to six months. In one case of organic psychosis in which hysterectomy had previously been performed, amenorrhœa was, of course, present, but this case is not included in the above series. In analysing these cases it is found that in eight the first event was the onset of mental symptoms while in the other three cases the amenorrhœa appeared before the mental condition. In the latter category was one case each of mania, schizophrenia, and organic psychosis. It was also found that eight of the cases were nulliparous while only three had borne children.

Records regarding the reappearance of menstruation were available in only seven cases. In three of the others—depression, manic, and paranoid state—mental recovery ensued rapidly and the patients were discharged from hospital, while one case of organic psychosis died a few weeks after admission.

But in all of these seven cases available for consideration the amenorrhœa cleared up and the menses returned in a normal condition under general mental treatment in some cases amplified by thyro-ovarian extract, while mental recovery, at least temporary, occurred in only two cases, both schizophrenics. Of the other five cases, three were as before while two were mentally worse.

These findings raise a doubt as to how much the amenorrhœa in these cases is directly associated with the mental condition. They, further, do not bear out the statement, sometimes seen, that with the return of menses an improvement in the mental condition may be expected.

The statement, often made, that amenorrhœa tends to appear at the onset of any mental illness is certainly not supported by our findings; nor is another, that the return of menstruation is a favourable sign during an attack of insanity

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and often presages or accompanies recovery. It is further said that recovery from a mental disorder without the return of menstruation is of unfavourable import as regards the permanence of cure, but we have no data on which to judge the correctness of this.

It is generally agreed that, in melancholia, amenorrhœa is frequently or "almost always" (Ross) present; yet in this series we find it occurring in only three cases of melancholia out of 41 in menstrual life—7·4 per cent. In the cases of mania it was present in one out of 21 cases and this agrees with the accepted view that, in mania, amenorrhœa is not usual.

Dysmenorrhœa was present in six cases—3·2 per cent., while in the controls the proportion was 10 per cent. Only in this class of case have the numbers in the non-psychotic controls been the larger.

The associated mental conditions comprised two cases of mental deficiency and one case each of schizophrenia, alternating state, paranoid state, and psychoneurosis. In all these cases pelvic examination showed a normal physical state of affairs; in one case only was a small cervical mucous polyp present.

Regarding age, four were under 30 years, one was 38 and another 44 years; while all were unmarried and nulliparous.

In five cases the dysmenorrhœa occurred every month but in one case it appeared only three or four times yearly. It was difficult to obtain accurate information regarding the age of onset of the dysmenorrhœa especially in the two cases over 30 years of age. In four of the cases there was a clear history that an exacerbation of the mental symptoms occurred at menstruation; these were the manic depressive, the paranoid, and two cases of mental deficiency.

In three cases—paranoid, schizophrenia, and mental deficiency—dilatation of the cervix was performed. In the first two of these the mental condition was as before, although in the paranoid the menstrual exacerbations had cleared up, while in the third it was relieved. One case of mental deficiency was treated with sedatives at menstruation but the mental condition was unchanged. The psychoneurosis had no gynæcological treatment but her mental condition cleared up while the manic-depressive case has been in and out on several occasions with relapses. It was difficult to estimate the amount of improvement in the dysmenorrhœa, but in all the cases this appeared to happen to a greater or less degree.

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Irregular Menstruation, present in four cases, was associated with two cases of depression and one case of mania and of organic psychosis.

Irregular menstruation was also found in certain other cases associated with physical gynæcological lesions, but these cases do not call for consideration in this paper.

Irregular and Profuse Menstruation was present in three cases—mania, manic depressive, and mental deficiency. One of these cases showed occasional dysmenorrhœa, but this was not a marked feature.

Late onset of Menstruation was present in two cases. One of these, with schizophrenia, was 28 years of age; she had menstruated for the first time three months previous to admission to hospital and, on examination, a normal, nulliparous condition of the pelvic organs was found. Menstruation was regular and normal. The other was a case of melancholia, aged 35 years, whose first menses appeared at the age of 18. The mental illness developed shortly after puberty which appeared to be the precipitating factor. Now, after seven years, the mental condition was unchanged after several remissions, but there was no exacerbation at menstruation which was regular and normal.

A consideration of these findings shows that the incidence of functional menstrual abnormalities is greater amongst those the subject of mental disease than in the case of at least that part of the sane female population who are referred to the gynæcologist.

In the latter sample of the population, in only one such condition, dysmenorrhœa, is this generalisation reversed and this is rather to be expected.

Now, when the matter is regarded from the psychiatric point of view we find menstrual irregularities, as detailed above, occurring in this ratio:—

Affective Disorders—

Depressions	.	.	.	11	
Manics	.	.	.	9	
Alternating	.	.	.	4	
			—		24 cases
Schizophrenia	.	.	.	13	"
Paranoid State	.	.	.	6	"
Mental Deficiency	.	.	.	6	"
Organic Psychoses	.	.	.	3	"
Psychoneurosis	.	.	.	1	"
			—		53 cases.

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From this it would appear that the affective disorders, including the melancholias, form the largest group and this is in agreement with the findings of others. They represent 47 per cent. of the 53 cases and when we remember that affective disorders form 35 per cent. of the mental disorders met with in menstrual life, it is seen that their incidence is still high.

Now, when we consider schizophrenia we find the percentage incidence of this condition in the 53 cases to be 25, while in the cases in menstrual life there are 26 per cent. of these; so that the tendency in these cases to show menstrual irregularities is not greater than their general incidence. Again, with the paranoids, these represent 11 per cent. of the 53 cases showing menstrual lesions and 16.4 per cent. of mental disease in menstrual life; so that they exhibit rather a lesser relative tendency than the affective disorders and schizophrenics to show menstrual disorders.

The effect of *menstruation* as a factor in predisposing producing *exacerbations of mental symptoms* now falls to be considered.

In this connection it was found that in 36 cases, 19 per cent. of 187 cases, definite exacerbations of mental symptoms occurred at the time of menstruation. Some of these have been referred to when discussing dysmenorrhœa.

These 36 cases comprised:—

Schizophrenia	12 cases
Affective Disorders—	
Depressed	5
Manic	3
Manic Depressed	1
	— 9 "
Mental Deficiency	8 "
Paranoid State	7 "
	— 36 cases.

The first thing to be noted is the general proportion of these 36 cases of just under 20 per cent. From the published opinions of others one would have expected a higher proportion in this respect. Thus Icard (quoted by Ross) says that, "The menstrual function can, by sympathy . . . create a mental condition varying from a simple psychalgia . . . to actual insanity, to a complete loss of reason." But another Frenchman, Répond, has more recently reached the very opposite

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conclusion, that there is no real association between menstruation and mental exacerbations and that any such exacerbations observed at this time are merely accidental.

According to Ross, in 40 cases of mania, 25 showed marked increase of symptoms at this time but in melancholia the change is not so marked. In Mackenzie's cases 22 cases of mania out of 49 showed exaggeration of symptoms during menstruation while, of 32 cases of melancholia, 13 showed increased agitation or depression at some periods. Healey found an increase of excitement in 49 per cent. and of depression in 16.8 per cent. of his cases. These figures show a much higher incidence of exaggeration of mental symptoms at menstruation than is seen in our series.

Clouston stated that the actual outbreak of mental disorder is coincident with menstruation in a very large number of women: we have not been able to obtain sufficient data in this respect to express an opinion.

It will be seen that in our cases showing exacerbation of symptoms at menstruation, the largest group is the schizophrenics but that the difference in numbers between the four main groups represented is not really great. Other writers usually stress mania and melancholia in this respect although it is stated that cases of stupor are more stuporose than usual at menstruation. In cases of psychoneurosis it is stated that such conditions as kleptomania may occur only at the menstrual period.

The subject of *epilepsy* appears worthy of some consideration in view of the known association, in some cases, of the fits with menstruation. There were 6 cases of epilepsy in our 250 cases—2.4 per cent.—and of these 4 were nulliparous and 2 parous, one illegitimately so. The ages varied from 22 to 45 years and the duration of the epilepsy from six months to early childhood. Confusion, dementia, and imbecility had developed in three cases.

But our most important observation is that in none of these cases was the condition in any way exaggerated at the time of menstruation nor were fits seen to be more liable to occur at that time. Others, reporting much larger numbers of cases, have reached different findings. Thus, Healey, in 53 cases of menstrual age, found an increased fit incidence in 40 while 5 others showed fits only at the menstrual periods. He also had 3 cases in which fits ceased at the menopause and he

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quoted 2 others in which fits ceased after hysterectomy and oöphorectomy.

In general gynæcological practice cases in whom epilepsy appears, it may be only at menstruation, are encountered from time to time and it is the general experience that they are usually very difficult to treat. Of these six cases four improved, one recovered, one died.

It would be wrong to conclude this communication without acknowledging our appreciation of the constant help and encouragement which we have received in this work from Dr E. Goodall of Hove, lately Medical Superintendent of the Cardiff City Mental Hospital.

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DISCUSSION.

Professor Johnstone said he would like to express the indebtedness of the Society to Professor Strachan for coming to give them the results of his investigations.

Professor Johnstone had the advantage of having been allowed to glance over Professor Strachan's paper earlier in the day, and he had found it a considerable help to him in understanding a paper which contained a large mass of statistics. Professor Strachan had referred to the scanty literature which was available on the subject and to the lack of accurate observations made. Probably many investigators had begun the work and had become discouraged owing to the fact that the observations seemed to lead nowhere. That, at any rate, had been his own experience a good many years ago, when, along with a friend who was medical officer in Morningside Asylum, he had embarked on a somewhat similar investigation, which ultimately had been dropped because no definite results seemed to be forthcoming.

The figures which Professor Strachan had brought forward showed the association of different menstrual abnormalities with the main types of mental disease. He was a little surprised that in this connection Professor Strachan had made no mention of the work of the late Sir Frederick Mott. Many of those present would remember that some ten years or more previously, Sir Frederick Mott had

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delivered the Morrison Lectures at the Royal College of Physicians of Edinburgh on his research work which showed that dementia præcox was associated with degenerative processes in the interstitial cells of the sex glands. Mott came to the conclusion that degenerative changes both in the central nervous system and in these sex gland cells were really manifestations of a lack of vitality in the original ovum. He quoted Kraepelin as saying that an intoxication arising from disturbed function of the sex glands was an essential element in that disease. Professor Johnstone would like to know whether Mott's work was still regarded as sound.

To the Fellows of the Society as gynæcologists, the latter section of Professor Strachan's paper was of more immediate interest, namely, the relation of menstruation and its abnormalities to the mental state, and Professor Strachan's conclusions were most interesting in themselves and particularly so because they differed markedly from those reached by earlier investigators in the same field. He had looked up what was said upon the subject by a man who took a very wide view of gynæcology, Professor Graves of Harvard. Graves wrote that there was no doubt that all pathological, mental and nervous conditions might be aggravated during the menstrual period, and if, in addition, menstruation was abnormal the reaction on the nervous system was greatly increased. He stressed the fact that women with criminal or suicidal tendencies often showed their inclination at such times, a point which Professor Strachan only referred to in a single sentence about kleptomania.

Havlock Ellis said that Lombroso had found that of 80 women arrested for obstructing the police or for assault, only 9 were not menstruating at the time. Ellis mentioned seven gynæcologists, including the late Robert Barnes, as having noted the frequency of suicidal tendencies at the menstrual periods. Wynn Westcott found in his long experience as a coroner that of 200 cases of women who had committed suicide, the majority were either menstruating or were at the change of life, and, in Germany, Heller had found by post-mortem examination of 70 similar cases that 35 per cent. were menstruating while a considerable proportion of the remainder were either pregnant or in the puerperal condition.

Among the insane the fact is universally recognised that during the menstrual period the insane impulse becomes more marked, if indeed it may not appear only at that time. The melancholics are more depressed as Clouston puts it, "the maniacal more restless, the delusional more under the influence of their delusions in their conduct, those subject to hallucinations have them more intensely, the impulsive cases are more uncontrollable, the cases of stupor more stupid, and the demented tend to be excited."

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In view of the discrepancy between Professor Strachan's observations and those of the older observers, he would like to see Professor Strachan's work extended over a considerably larger number of cases before definite conclusions were drawn. With regard to epilepsy, Professor Johnstone's own limited experience led him to agree with Professor Strachan, and he thought that there were very few cases in which the association of the fits with the menstrual periods was so clear and so exclusive as to justify such operations as castration.

In general, with regard to treatment, he thought that insane women with gynæcological conditions requiring treatment should be treated in exactly the same way as sane women. Sometimes the results would prove beneficial to the mental condition, but in the experience of most gynæcologists that was unfortunately not the case.

Dr Angus MacNiven expressed his gratitude to the Society for inviting him to be present. He was interested in Professor Strachan's paper, as he was in Cardiff City Mental Hospital when Professor Strachan began the work. He said that any casual observations he had made himself confirmed Professor Strachan's conclusions, that menstrual disorders were not very much more frequent in the insane than they were in the sane population, and where menstrual disorders existed they bore little relation to the mental condition, and an improvement in the menstrual disorder did not always bring about an improvement in the mental state. He wondered why the old observers found menstrual disorders so frequent in cases of mental illness. It was generally admitted that conditions in mental hospitals were now much better than they were in the past. Patients were better looked after and better fed. In consequence the general health of patients in institutions had improved. Might it not be that the high incidence of menstrual disorder noticed by the older observers was due to the poor standard of physical health of the patients with whom they were dealing? Dr Strachan mentioned that certain cases, especially cases of mania, showed an aggravation of their symptoms at the time of menstruation. This is what one would expect, as these cases showed a general increased irritability, and were in consequence very sensitive to any change in themselves or in their environment. On the other hand, cases of melancholia were, as a rule, insensitive to stimuli, and, as one would expect, menstruation did not produce any variation in their mental condition. Professor Johnstone had referred to Sir Frederick Mott's work on the causation of dementia præcox. He (the speaker) thought that now Mott's conclusions were not generally accepted. Whatever the cause of dementia præcox might be, it was not primarily due to organic changes occurring in the endocrine glands. It was true, however, that certain cases of dementia præcox showed signs of immaturity in their physical development. The appearance of

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these cases was striking. They looked much younger than their years. He had known a woman of 34 look like a girl of 18. There was no intellectual defect in these cases, but emotionally the patient was childish. He thought that in these cases the sexual organs were not fully developed. The speaker then referred to a paper by Farrar and Franks in a recent number of the *American Journal of Psychiatry*. The writers of this paper discussed the relation of the menopause to the causation of mental disorder. Their conclusions were that no particular form of mental disease was associated with the menopause. Mental disease occurring at that period might occur at any other time of life. They suggested, however, that the menopause might act indirectly as a causative agent in producing mental disorder, because there was a general belief that at this period a woman was almost certain to experience mental and physical disturbances. A result of this popular belief was that many women looked forward with apprehension to the change of life, and a state of anxiety was engendered which might very well be a contributing factor in producing a mental break-down.

Dr Buist said he thought the key to the very interesting results *Dr Strachan* had put before them lay in the fact that he had started out not expecting to come to some known conclusion but to find the facts. He considered that accuracy and absence of prejudice were of great importance in such work, and from that point of view *Dr Strachan's* paper was very much appreciated.

The President admitted that he had been just a little disappointed with the method of approach *Professor Strachan* had adopted. He had expected that he would have dealt with the etiological relationship between gynæcological disease and mental defects. After hearing his paper, however, he quite realised the difficulty of such a study until we had knowledge of some preliminary essential facts and it was this knowledge that *Professor Strachan* had attempted to obtain.

Professor Johnstone raised an interesting question when he referred to epilepsy. Considerable difficulty was always found with regard to questions of essential diagnosis. In such cases one could sometimes trace quite clearly a relationship between menstruation and epilepsy. *Dr Young* had seen several cases of this condition, but that type of case had apparently not come under *Professor Strachan's* observation at all, either, presumably, because they did not find their way into an asylum, or because by that time, the time relationship had become obscure.

Dr Strachan (in reply) thanked the Society for the very warm welcome he had received.

Professor Johnstone remarked that the paper contained a large number of figures. It was extremely difficult to make a paper of that

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(Kind interesting, but it was necessary to have such figures so one had just to go through with it. Obviously he said, a certain amount of the paper was the work of Dr Skottowe who is a specialist in mental diseases. He had not referred to the work of Novak from the point of view of criticism. He had purposely excluded organic lesions from his paper—had he included these the communication would have been much too long: neither had Sir Frederick Mott's work been mentioned for this reason, but he thought anyone reading it now would have difficulty in understanding the gynæcological pathology. Mott had considerable opportunities for performing post-mortem examinations. Dr Strachan had discussed his work from a clinical point of view.

Dr MacNiven mentioned under-development. Dr Strachan was always very slow to accept conditions of hypofunction. His experience was, taking for example a case of dysmenorrhœa in the nullipara, that you examined the uterus which appeared in a large proportion of cases to be extremely small, and you were apt to think the uterus under-developed, but when you passed a sound into that uterus, often the length of the cavity was found to be a full $2\frac{1}{2}$ inches and, from the clinical point of view, one had to be very careful.

He thoroughly agreed with Professor Johnstone, that the treatment of these cases with menstrual disorders should be treated in the insane just as in the sane women. With regard to the cases of epilepsy, in this series there were no exacerbations at menstruation. In his own private practice, however, he had two cases whose history was that they were subject to epilepsy at, and only at, menstruation.

In conclusion, these cases were investigated from the psychiatric point of view, and then from the gynæcological point of view independently. They did not want to be biased, and it was of interest that their results differed so much from others.

